

ACNR

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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

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Joint meeting of the ABN and Neurology Section, Cuban Society of Neurology & Neurosurgery.

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Think
beyond
efficacy...

...when looking for additional seizure control

▼ zonegran® χ^2
zonisamide
Beyond efficacy

Zonegran is indicated as adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation.

PRESCRIBING INFORMATION

Zonegran®▼ (zonisamide)

Please refer to the SPC before prescribing.

Presentation: Hard capsules: 25 mg, 50 mg, 100 mg zonisamide. **Indication:** Adjunctive therapy in adult patients with partial seizures, with or without secondary generalisation. **Dose and administration: Adults:** Starting dose is 50 mg in two divided doses. After one week, increase to 100 mg daily. Then increase at one weekly intervals in 100 mg increments. Can be taken once or twice daily after titration. In renal or hepatic impairment and patients not receiving CYP3A4-inducing agents consider two weekly intervals. Withdraw gradually. **Elderly and patients with renal or hepatic impairment:** Caution. Not recommended in severe hepatic impairment. **Children and adolescents under 18 years:** Not recommended. **Contraindications:** Hypersensitivity to zonisamide, sulphonamide or any excipient. **Pregnancy:** Do not use during pregnancy unless potential benefits justify the risks. Women of childbearing potential must use contraception during treatment and for one month after discontinuation. **Lactation:** Excreted into breast milk. Either discontinue Zonegran or stop breastfeeding. **Warnings and precautions:** Serious rashes occur, including cases of Stevens-Johnson syndrome. Contains a sulphonamide group which is associated with serious immune based adverse reactions. Closely supervise and consider discontinuation in patients with unexplained rash. Cases of agranulocytosis, thrombocytopenia, leukopenia, aplastic anaemia, pancytopenia and leucocytosis have been reported. Monitor for signs of suicidal ideation and behaviours and consider appropriate treatment. Use with caution in patients with risk factors for nephrolithiasis, including prior stone formation, family history of nephrolithiasis and hypercalcaemia. Evaluate and monitor serum bicarbonate levels in patients who are

at risk of metabolic acidosis. If metabolic acidosis develops and persists, consider reducing the dose, discontinuing or alkali treatment. Use with caution in patients treated with carbonic anhydrase inhibitors, e.g. topiramate. Decreased sweating, elevated body temperature and heat stroke have been reported. Patients should maintain hydration and avoid excessive temperatures. Monitor pancreatic lipase and amylase levels in patients taking Zonegran who develop clinical signs and symptoms of pancreatitis, consider discontinuation. In cases of severe muscle pain/weakness with or without fever, assess markers of muscle damage and consider discontinuation. Zonegran 100 mg capsules contain E110. Caution in patients less than 40 kg. In patients with weight loss consider dietary supplement, increased food intake or discontinuation. **Drug interactions:** No clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, sodium valproate, oral contraceptives (ethinylestradiol or norethisterone). Insufficient data with carbonic anhydrase inhibitors, e.g. topiramate. Zonegran was not affected by lamotrigine or CYP3A4 inhibitors. Caution with drugs which are P-gp substrates. Avoid concomitant administration with drugs causing urolithiasis. Zonisamide is metabolised partly by CYP3A4, N-acetyl-transferases and conjugation with glucuronic acid; therefore caution with substances that can induce or inhibit these enzymes. **Side effects:** Most common adverse reactions in controlled adjunctive-therapy studies were somnolence, dizziness and anorexia. Refer to SPC for all side effects. Very common effects ($\geq 1/10$): anorexia, agitation, irritability, confusional state, depression, ataxia, dizziness, memory impairment, somnolence, diplopia, decreased bicarbonate. Common effects ($\geq 1/100$, $< 1/10$): ecchymosis, hypersensitivity, affect

libility, anxiety, insomnia, psychotic disorder, bradyphrenia, disturbance in attention, nystagmus, paraesthesia, speech disorder, tremor, abdominal pain, constipation, diarrhoea, dyspepsia, nausea, rash, nephrolithiasis, fatigue, influenza-like illness, pyrexia, weight decreased. Serious effects: pneumonia, suicidal attempt, convulsion, cholecystitis, calculus urinary. Isolated cases of Sudden Unexplained Death in Epilepsy Patients (SUDEP). Post-marketing data suggests patients aged ≥ 65 years report a higher frequency of Stevens-Johnson syndrome and Drug Induced Hypersensitivity syndrome. **Legal category:** POM. **Basic UK NHS cost:** Zonegran 25 mg: packs of 14 £8.82, Zonegran 50 mg: packs of 56 £47.04, Zonegran 100 mg: packs of 56 £62.72. **Irish price to wholesaler:** Zonegran 25 mg: packs of 14 €9.20, Zonegran 50 mg: packs of 56 €48.78, Zonegran 100 mg: packs of 56 €65.18. **Marketing authorisation numbers:** Zonegran 25 mg 14 capsules: EU/1/04/307/001, Zonegran 50 mg 56 capsules: EU/1/04/307/003, Zonegran 100 mg 56 capsules: EU/1/04/307/004. **Marketing authorisation holder:** Eisai Ltd. **Further Information from/Marketed by:** Eisai Ltd, European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN. **Date of preparation:** Jan 2011

Adverse events should be reported. Reporting forms and Information can be found at www.yellowcard.gov.uk Adverse events should also be reported to Eisai Ltd on 0208 600 1400/ 0845 676 1400 or Lmedinfo@eisai.net

Date of Preparation: April 2011

Zonegran-UK2381

New – Gilenya an MS treatment that's oral

Prior IFN treatment

Failed response
to full and
adequate course



Relapse

Unchanged or
increased rate, or
ongoing severe
relapses



Prescribe Gilenya

Once daily
oral MS therapy



NOVARTIS

Abbreviated Prescribing Information: GILENYA® (fingolimod)

Important note: Before prescribing, consult Summary of Product Characteristics (SmPC). **Presentation:** Hard capsule containing 0.5 mg fingolimod (as hydrochloride). **Indications:** Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:

- Patients with high disease activity despite treatment with a beta-interferon. These patients may be defined as: those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI. **Dosage: Adults:** Treatment should be initiated and supervised by a physician experienced in multiple sclerosis. One 0.5 mg capsule to be taken orally once daily. Patients can switch directly from beta-interferon or glatiramer acetate to Gilenya provided there are no signs of relevant treatment-related abnormalities, e.g. neutropenia. Use with caution in patients aged 65 years and over. Safety and efficacy of Gilenya in children up to 18 years has not been established. No dose adjustments required in patients with mild to severe renal impairment or mild to moderate hepatic impairment. Exercise caution in patients with mild to moderate hepatic impairment. Do not use in patients with severe hepatic impairment (Child-Pugh class C). Use with caution in patients with diabetes mellitus due to an increased risk of macular oedema. **Contraindications:** Known immunodeficiency syndrome, patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies), severe active infections, active chronic infections (hepatitis, tuberculosis), known active malignancies, except for patients with cutaneous basal cell carcinoma, severe liver impairment (Child-Pugh class C), hypersensitivity to the active substance or to any

of the excipients. **Warnings/Precautions: Bradycardia:** Initiation of treatment results in a transient decrease in heart rate which may be associated with atrioventricular conduction delays. Observe all patients for 6 hours for bradycardia. In the event of bradycardia-related symptoms, initiate appropriate clinical management and observe until symptoms resolve. The same precautions apply if Gilenya is discontinued for more than 2 weeks. Gilenya has not been studied in patients with sitting heart rate <55 beats per minute, second degree or higher AV block, sick-sinus syndrome, ischaemic cardiac disease, congestive heart failure, significant cardiovascular disease, a history of syncope or those taking beta blockers. Seek advice from a cardiologist before initiation of treatment in these patients. Gilenya should not be co-administered with class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products. Exercise caution at treatment initiation in patients receiving beta blockers, or other substances which may decrease heart rate (e.g. verapamil, digoxin, anticholinesteratic agents or pilocarpine) due to possible additive effects. Avoid medicinal products that may prolong QTc interval. **Infections:** Reduction of the lymphocyte count to 20-30% of baseline values occurs with Gilenya. Perform a complete blood count (CBC) at baseline, and periodically during treatment, and in case of signs of infection, stop Gilenya until recovery if absolute lymphocyte count $<0.2 \times 10^9/L$ is confirmed. Consider VZV vaccination of patients without a history of chickenpox or VZV antibody negative patients prior to commencing Gilenya. Gilenya may increase the risk of infections. Employ effective diagnostic and therapeutic strategies in patients with symptoms of infection while on Gilenya and for 2 months after discontinuation. **Macular oedema:** Macular oedema with or without visual symptoms has been reported in patients taking Gilenya. Perform an ophthalmological evaluation 3-4 months after Gilenya initiation. Evaluate the fundus, including the macula in patients reporting visual disturbances. Perform ophthalmological evaluation prior to initiating therapy and periodically thereafter in patients with diabetes mellitus or a history of uveitis. Discontinue Gilenya if a patient develops macular oedema. **Liver function:** Do not use Gilenya in patients with severe pre-existing hepatic injury (Child-Pugh class C). Delay Gilenya initiation in patients with active viral hepatitis until resolution. Recent transaminase and bilirubin levels should be available before initiation of Gilenya. Monitor liver transaminases at months 1, 3 and 6 and periodically thereafter. Institute more frequent monitoring if transaminases rise above 5 times the ULN, including serum



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A new perspective in MS

bilirubin and alkaline phosphatase (ALP) measurement. Stop Gilenya treatment with repeated confirmation of liver transaminases above 5 times the ULN and only re-commence once liver transaminase values have normalised. Patients with symptoms of hepatic dysfunction should have liver enzymes checked and discontinue Gilenya if significant liver injury is confirmed. Resume Gilenya only if another cause of liver injury is determined and if the benefits of therapy outweigh the risks. Exercise caution with Gilenya use in patients with a history of significant liver disease. **Serological testing:** Peripheral blood lymphocyte counts cannot be utilised to evaluate the lymphocyte subset status of a patient treated with Gilenya. Laboratory tests involving the use of circulating mononuclear cells require larger blood volumes due to reduction in the number of circulating lymphocytes. **Blood pressure effects:** Gilenya can cause a mild increase in blood pressure. Monitor blood pressure regularly during Gilenya treatment. **Respiratory effects:** Use Gilenya with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease due to minor reductions in values for forced expiratory volume (FEV₁) and diffusion capacity for carbon monoxide (DLCO). **Prior immunosuppressant treatment:** No washout is necessary when switching patients from interferon or glatiramer acetate to Gilenya assuming any immune effects (e.g. neutropenia) have resolved. Exercise caution when switching patients from natalizumab to Gilenya owing to the long half life of natalizumab and concomitant immune effects. **Stopping therapy:** Gilenya is cleared from the circulation in 6 weeks. Caution is indicated with the use of immunosuppressants soon after the discontinuation of Gilenya due to possible additive effects on the immune system. **Interactions:** Anti-neoplastic, immunosuppressive or immune-modulating therapies should not be co-administered due to the risk of additive immune system effects. Exercise caution when switching patients from long-acting therapies with immune effects, e.g. natalizumab or mitoxantrone. No increased rate of infection was seen with concomitant treatment of relapses with a short course of corticosteroids. Vaccination may be less effective during and for up to 2 months after Gilenya treatment. Avoid use of live attenuated vaccines due to infection risk. Due to additive effects on heart rate, exercise caution when initiating Gilenya in patients receiving beta blockers, or class Ia and III antiarrhythmics, calcium channel blockers like verapamil or diltiazem, digoxin, anticholinesteratic agents or pilocarpine. Caution is indicated with substances that may

inhibit CYP3A4. Co-administration of fingolimod with ketoconazole increases fingolimod exposure. No interaction has been observed with oral contraceptives when co-administered with fingolimod. **Fertility, pregnancy and lactation:** There is potential for serious risk to the fetus with Gilenya. A negative pregnancy test is required before initiation of Gilenya. Female patients must use effective contraception during treatment with Gilenya and for 2 months after discontinuation. Discontinue Gilenya if a patient becomes pregnant. Fingolimod is excreted into breast milk. Women receiving Gilenya should not breast feed. Fingolimod is not associated with a risk of reduced fertility. **Undesirable effects:** *Very common* ($\geq 1/10$): Influenza viral infections, headache, cough, diarrhoea, increased alanine transaminase (ALT), back pain. *Common* ($\geq 1/100$ to $< 1/10$): herpes viral infections, bronchitis, sinusitis, gastroenteritis, tinea infections, lymphopenia, leucopenia, depression, dizziness, parasthesia, migraine, blurred vision, eye pain, bradycardia, atrioventricular block, hypertension, dyspnoea, eczema, alopecia, pruritus, asthenia, increased gamma-glutamyl transferase (GGT), increased hepatic enzymes, abnormal liver function test, increased blood triglycerides, decreased weight. *Uncommon* ($\geq 1/1,000$ to $< 1/100$): pneumonia, macular oedema, decreased neutrophil count. **Packs and price:** Perforated unit dose blister packs containing 7 x 0.5 mg hard capsules: £367.50. Blister packs containing 28 x 0.5 mg hard capsules: £1470. **Legal classification:** POM. **Marketing Authorisation Holder:** Novartis Europharm Ltd, Wimblehurst Rd, Horsham, W Sussex, RH12 5AB, UK. **Marketing Authorisation Numbers:** 7 x 0.5 mg hard capsules: EU/1/11/677/001, 28 x 0.5 mg hard capsules: EU/1/11/677/005 **Date of last revision of prescribing information:** March 2011. **Full Prescribing Information available from:** Novartis Pharmaceuticals UK LTD, Frimley Business Park, Frimley, Surrey, GU16 7SR. Tel: (01276) 692255 Fax: (01276) 692508.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Novartis (01276) 698370

Date of preparation: March 2011 Code: FIN11-102

Editorial board and contributors



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Stephen Kirker is the editor of the Rehabilitation Section of ACNR and Consultant in Rehabilitation Medicine in Addenbrooke's NHS Trust, Cambridge. He trained in neurology in Dublin, London and Edinburgh before moving to rehabilitation in Cambridge and Norwich. His main research has been into postural responses after stroke. His particular interests are in prosthetics, orthotics, gait training and neurorehabilitation.



Boyd Ghosh is the Editor of our Conference News section. He is currently a Specialist Registrar in Southampton having completed a PhD in Cambridge in cognitive neuroscience. His special interests are cognition and movement disorders, with a particular interest in progressive supranuclear palsy. He is currently secretary for the ABN trainees committee.



Rhys Davies is the editor of our Book Review Section. He is a consultant neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool and at Ysbyty Gwynedd in Bangor, North Wales. He has a clinical and research interest in cognitive neurology.



Alastair Wilkins is our Case Report Co-ordinator. He is Senior Lecturer in Neurology and Consultant Neurologist, University of Bristol. He trained in Neurology in Cambridge, Norwich and London. His research interests are the basic science of axon degeneration and developing treatments for progressive multiple sclerosis.



Peter Whitfield is ACNR's Neurosurgery Editor. He is a Consultant Neurosurgeon at the South West Neurosurgery Centre, Plymouth. His clinical interests are wide including neurovascular conditions, head injury, stereotactic radiosurgery, image guided tumour surgery and lumbar microdiscectomy. He is an examiner for the MRCS and is a member of the SAC in neurosurgery.



Heather Angus-Leppan is ACNR's ABN representative on the Editorial Board. She is Head of the Neurology Department at Barnet Hospital and Consultant Neurologist, Honorary Senior Lecturer and Epilepsy Lead at the Royal Free Hospital, London, UK. She is the Honorary Assistant Secretary of the Association of British Neurologists, Honorary Secretary of the Neurosciences Section of the Royal Society of Medicine and current Chair of the Map of Medicine Epilepsy Group, UK.

International editorial liaison committee

Professor Riccardo Soffietti, Italy: Chairman of the Neuro-Oncology Service, Dept of Neuroscience and Oncology, University and S. Giovanni Battista Hospital.

Professor Klaus Berek, Austria: Head of the Neurological Department of the KH Kufstein.

Professor Hermann Stefan, Germany: Professor of Neurology /Epileptology in the Department of Neurology, University Erlangen-Nürnberg.

Professor Nils Erik Gilhus, Norway: Professor of Neurology at the University of Bergen and Haukeland University Hospital.

Professor Giles Hardingham wins award

Professor Giles Hardingham has been named as the 2011 recipient of the International Society for Neurochemistry Young Scientist Lectureship Award. The awards are to recognise the research achievements of promising young scientists involved in neurochemical research.



Gowers Awards 2011 – Submissions invited

1. Gowers Young Physician Award (£500): A dissertation on any aspect of epilepsy.
2. Gowers Medical Student Award (£500): A dissertation on any aspect of epilepsy, including case histories of a patient personally observed by the student.
3. Gowers Combined Nursing & Health Professional Award (£500): A dissertation on any aspect of epilepsy, by a member of the nursing profession or recognised health profession related to epilepsy care.

Deadline: Friday 26th August

For more information contact Ms Juliet Solomon, Email: members@ilae-uk.org.uk.

Download details and Gowers Essay Forms from: www.ilae-uk.org.uk

Professor Rodrigo Quian Quiroga receives £30k grant

University of Leicester Professor of Bioengineering Rodrigo Quian Quiroga has received a grant of £30K from the "Beyond Text" initiative of the Arts and Humanities Research Council (AHRC). "The links between science and arts have so far been very limited," said Professor Quiroga, whose discovery of a type of neuron in the brain which fires in an 'abstract' manner to different pictures of familiar persons, including celebrities like Jennifer Aniston or Halle Berry, has been internationally acclaimed, and whose work has also indicated that it is possible to tell what people are seeing from their neuronal activity. The grant will enable him to continue his quest into these fascinating mysteries in the company of Dr Sandra Dudley, expert in material and visual culture and the senses in Leicester's School of Museum Studies, and with the renowned Argentine artist, Mariano Molina. The project will culminate in an "Arts & Science" exhibition in the autumn.

For more information visit: www.le.ac.uk/neuroengineering



New Consultancy Appointment

Rob Powell has been appointed as Consultant Neurologist at Morriston Hospital in Swansea.



New Conference News Editor for ACNR

ACNR is delighted to welcome Boyd Ghosh as Conference News Editor. Boyd has had rather a circuitous path to medicine, having initially started life as a physicist, before becoming a manager of a home for people with learning disabilities and later the coordinator for the Crisis at Christmas homeless shelters. He completed his medical degree in the newly merged St Bartholomew's and the Royal London medical schools and developed an interest in Neuroscience. He completed a PhD in cognitive neuroscience with James Rowe and John Hodges at Cambridge. Boyd is currently a trainee in Southampton, and after "modernising medical careers" takes an active interest in the structure of neurology in the UK, by acting as secretary for the ABN trainees committee. He is also continuing his research interests in progressive supranuclear palsy and cognition. As is true for many readers, money for him to attend conferences without the benefit of academic grants is sparse. In his new role as Conference News Editor, Boyd is particularly interested in highlighting conferences which readers would have liked to attend if time and money allowed.





Image: Peter Fraser

*When you've got MS, just opening
a bottle can be a reason to celebrate.*

MS can make simple, everyday tasks difficult or impossible. Adding Sativex to existing spasticity treatment can improve symptoms like stiffness and spasm, helping to make daily life easier for people with MS.

Another Small Victory for Sativex

Instead of leaving the Sativex prescribing information at the foot of the page, we've put it where you can't miss it. Please take a look. After all, these are the crucial details that will help you decide if Sativex can help your MS patients.

Sativex® Oromucosal Spray Prescribing Information (refer to full Summary of Product Characteristics (SmPC) before prescribing). **Presentation:** 1mL contains: 38-44mg and 35-42mg of two extracts from *Cannabis sativa* L., (Cannabis leaf and flower) corresponding to 27mg delta-9-tetrahydrocannabinol (THC) and 25mg cannabidiol (CBD). Each 100 microlitre spray contains: 2.7mg THC and 2.5mg CBD. **Indication(s):** as add-on treatment, for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy. **Posology and method of administration:** oromucosal use only. Treatment must be initiated and supervised by a physician with specialist expertise in MS. Direct spray at different sites on the oromucosal surface, changing site for each use of product. May take up to 2 weeks to find optimal dose, review response after 4 weeks of treatment. Re-evaluate long term treatment periodically.

Adults: titration period necessary; number/timing of sprays will vary between patients. Number of sprays increased daily according to SmPC table, up to maximum of 12 sprays per day with minimum 15 minutes between sprays. **Children and adolescents:** not recommended. **Elderly:** no specific studies but CNS side effects may be more likely (see Warnings and precautions) **Significant hepatic or renal impairment:** no specific studies but effects of Sativex may be exaggerated or prolonged. Frequent clinical evaluation recommended. **Contra-indications:** hypersensitivity to cannabinoids or excipients. Breast feeding. Known/suspected history or family history of schizophrenia/other psychotic illness. History of severe personality disorder/other significant psychiatric disorder other than depression due to underlying condition. **Warnings and precautions:** not recommended in patients with serious cardiovascular disease. Caution in patients with history of epilepsy/recurrent seizures. THC and CBD are metabolised in the liver. Several THC metabolites may be psychoactive. Contains approx. 50% v/v ethanol. Risk of falls if spasticity/muscle strength no longer sufficient to maintain posture/gait. CNS side effects e.g. dizziness, somnolence could impact personal safety, e.g. hot food and drink preparation. Theoretical risk of additive effect with muscle-relaxing agents, not seen in clinical trials but warn patients risk of falls may increase. No effect seen on fertility but cannabinoids shown to affect spermatogenesis in animals. Female patients of child-bearing potential/male patients with a partner of child-bearing potential should use reliable contraception. Patients with a history of substance abuse may be more prone to abuse Sativex. Withdrawal symptoms following abrupt withdrawal of long-term Sativex are likely to be limited to transient disturbances of sleep, emotion or appetite. No increase in daily dosage observed in long-term use; self-reported levels of 'intoxication' low; dependence on Sativex unlikely. **Interactions:** no clinically apparent

drug-drug interactions seen. Co-administration with food results in mean increase in C_{max} , AUC and half-life (increase less than between-subject variability in these parameters). Concomitant ketoconazole increases C_{max} and AUC of THC (and primary metabolite) and CBD. Increase less than between-subject variability. Risk of additive sedation and muscle relaxing effects with hypnotics, sedatives and drugs with sedating effects. **Pregnancy and lactation:** do not use in pregnancy unless benefit outweighs potential risks. Do not use if breast feeding. Insufficient experience of effects on reproduction - use reliable contraception during therapy and for 3 months after discontinuation. **Effects on ability to drive and use machines:** do not drive, operate machinery or engage in any hazardous activity if experiencing significant CNS side effects; warn patients may cause loss of consciousness. **Side effects:** very common - dizziness, fatigue; common - anorexia, decreased or increased appetite, depression, disorientation, dissociation, euphoria, amnesia, balance disorder, disturbance in attention, dysarthria, dysgeusia, lethargy, memory impairment, somnolence, blurred vision, vertigo, constipation, diarrhoea, dry mouth, glossodynia, mouth ulceration, nausea, oral discomfort/pain, vomiting, application site pain, asthenia, feeling abnormal/ drunk, malaise, fall; uncommon - hallucination, illusion, paranoia, suicidal ideation, delusional perception, syncope, palpitations, tachycardia, hypertension, pharyngitis, throat irritation, upper abdominal pain, oral mucosal disorders e.g. discolouration, exfoliation, stomatitis, tooth discolouration, application site irritation; unknown frequency - psychiatric symptoms e.g. anxiety and mood changes, transient psychotic reactions, possible leukoplakia (unconfirmed); inspect oral mucosa regularly in long term use.



Prescribers should consult the SmPC for further information on side effects. **Overdose:** symptomatic and supportive treatment required. **Special precautions for storage:** refrigerate (2 to 8°C); once opened refrigeration is unnecessary but do not store above 25°C. **Legal Category:** POM **Package quantities and basic NHS costs:** 3 x 10mL £375.00. **MA holder:** GW Pharma Ltd, Porton Down Science Park, Salisbury, Wiltshire SP4 0JQ **MA number(s):** PL 18024/0009 **Further information available from:** Bayer Schering Pharma, Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA United Kingdom. Telephone: 01635 563000. **Date of preparation:** March 2010.

Sativex® is a registered trademark of GW Pharma Ltd.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to GW Pharma Ltd. Tel: 01353 616636, Fax: 01353 616638

SATIVEX®
delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)

The cause of brief episodes of isolated amnesia in patients attending neurology clinics often distils down to one of whether they had had an episode of Transient Global Amnesia (TGA) or Transient Epileptic Amnesia (TEA). This latter condition is the subject of the review by Chris Butler and Adam Zeman in this issue of the ACNR – authors who have done much to help better understand this condition. It is therefore no surprise to find that this article is rich in useful data and advice.

Nils Erik Gilhus and colleagues, in the first in a new series on Neuroscience and Neurology Research from Norway explain that myasthenia gravis (MG) is not just a disorder of the neuromuscular junction but has antigen targets in the muscle itself. In particular they discuss the significance of antibodies to the ryanodine receptor and the structural protein Titin in patients with MG, not only in terms of pathophysiology but also as markers of disease subtypes.

“Dear Neurologist, Many thanks for seeing this 38-year-old woman with a fixed abnormal posture of the right hand and arm that began 12 years ago after she sprained her wrist in what seemed to be a simple injury. She has been extensively investigated and no cause has been found. She is in severe pain and nothing has helped. She has been to see an orthopaedic surgeon who has suggested he could amputate the limb above the elbow, and she is seriously considering this option.” What would your advice to her be? Mark Edwards discusses this in the latest of our articles in the Neuropsychiatry series.

This year my skull sutures will eventually close for good, but up to this point much can be deduced by looking at the physical size of the head as Angeliki Menounou writes in her article. The causes of macro- and microcephaly are discussed and the best way to investigate them laid out in useful tables and figures, along with a more lengthy discussion on types of autosomal recessive primary microcephaly (MCPH).

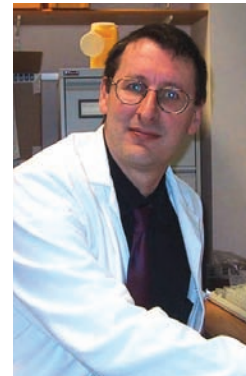
The UK is second only to Ireland in terms of having the lowest number of medical rehabilitation consultants per head of population in Europe, and this may explain why much of what we do in rehabilitation lags behind other countries. Mohab Gaid in a report produced by the Royal College of Physicians and the British Society of Rehabilitation Medicine, takes us through the issues of rehabilitation medicine that need addressing in order to make the services we provide work better and more efficiently, especially as we head towards a new era of health care commissioning.

How do you obtain informed consent from patients with aphasia? This is the challenge that Rebecca Palmer and Gail Patterson have taken on and which they have attempted to answer through a NIHR Research for Patient Benefit funded project. They conclude that there are ways to do this, and provide several examples of what this might look like.

Andrew Larner, in another in his series on headache, concentrates on Russian literature for his source of information in this new article including Bulgakov, Tolstoy and Chekhov.

We all have those worrying moments when we cannot quite remember what we have done but in our Personal Perspectives piece, Dr Mary Catanazaro explains that in her case it was secondary to complex partial seizures. This led to problems with employment and a host of other issues before she was successfully operated on at the age of 53 and the scar tissue in her right amygdala excised.

We have our usual section of reviews and I am pleased to announce that Dr Boyd Ghosh has taken on the editing of the conference reviews section of ACNR. If you would like to contribute a conference review, please contact Boyd via the Publisher Rachael Hansford, email Rachael@acnr.co.uk ◆



Roger Barker, Co-Editor.

*Roger Barker, Co-Editor,
Email: Rachael@acnr.co.uk*

Life with epilepsy can be much more than just a gap between seizures

It's hard to live life to the full if part of you is always expecting the next seizure. VIMPAT® is an anti-epileptic drug with an innovative mode of action.^{1,2} In clinical trials, VIMPAT® has shown improved seizure control when added to first and second generation AEDs.³ Prescribe VIMPAT® when you want your patients to look forward with the confidence of additional seizure control.^{1,3}


VIMPAT®
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PRESCRIBING INFORMATION (Please consult the Summary of Product Characteristics (SPC) before prescribing.) **Vimpat® Lacosamide Active Ingredient:** Tablets: lacosamide 50 mg, 100 mg, 150 mg and 200 mg. Syrup: lacosamide 15 mg/ml. **Solution for infusion:** lacosamide 10 mg/ml. **Indication:** Vimpat is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older. **Dosage and Administration:** Adults and adolescents from 16 years: Recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after 1 week. Maximum daily dose of 400 mg (in two 200 mg doses). **For solution for infusion:** Infused over a period of 15 to 60 minutes twice daily. Can be administered i.v. without further dilution. **Elderly:** No dose reduction necessary. Age associated decreased renal clearance with an increase in AUC levels should be considered. **Paediatric patients:** Not recommended. **Patients with renal impairment:** No dose adjustment necessary in mild and moderate renal impairment. Dose adjustment is recommended for patients with severe renal impairment and patients with end-stage renal disease (see SPC). Dose titration should be performed with caution. **Patients with hepatic impairment:** No dose adjustment needed in mild to moderate impairment. In accordance with current clinical practice, if Vimpat has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week). **Contraindications, Warnings, etc:** Contraindications:

Hypersensitivity to lacosamide or to any of the excipients. Known second- or third-degree atrioventricular block. In addition for tablets, hypersensitivity to peanuts or soya. **Precautions:** Lacosamide has been associated with dizziness. Use with caution in patients with known conduction problems, severe cardiac disease or in elderly. Excipients in the syrup may cause allergic reactions (possibly delayed), should not be taken by those with fructose intolerance and may be harmful to patients with phenylketonuria. Monitor patients for signs of suicidal ideation and behaviours. Advise patients and carers to seek medical advice should such signs emerge. **Interactions:** Prolongations in PR interval with lacosamide have been observed in clinical studies. Use with caution in patients treated with products associated with PR prolongation and those treated with class I antiarrhythmic drugs. Strong enzyme inducers such as rifampicin or St John's Wort may moderately reduce the systemic exposure of lacosamide. No significant effect on plasma concentrations of carbamazepine and valproic acid. Lacosamide plasma concentrations were not affected by carbamazepine and valproic acid. No clinically relevant interaction with ethinylestradiol and levonorgestrel. No effect on pharmacokinetics of digoxin. **Pregnancy and Lactation:** Should not be used during pregnancy. For precautionary measures, breast feeding should be discontinued during treatment with lacosamide. **Driving etc.:** Patients are advised not to drive a car or operate other potentially hazardous machinery until they are familiar with the effects of Vimpat on their ability to perform such activities. **Adverse Effects:** Very common (≥10%): Dizziness, headache, diplopia, nausea. Common (between 1%-10%): Depression, balance disorder, abnormal coordination,

memory impairment, cognitive disorder, somnolence, tremor, nystagmus, blurred vision, vertigo, vomiting, constipation, flatulence, pruritus, gait disturbance, asthenia, fatigue, fall, skin laceration. Adverse reactions associated with PR prolongation may occur. Consult SPC in relation to other side effects. **Pharmaceutical Precautions:** Tablets: None. Syrup: Do not store above 30°C. Use within 4 weeks of first opening. **Solution for infusion:** Do not store above 25°C. Use immediately. **Legal Category:** POM. **Marketing Authorisation Number(s):** 50 mg x 14 tabs: EU/1/08/470/001; 100 mg x 14 tabs: EU/1/08/470/004; 100 mg x 56 tabs: EU/1/08/470/005; 150 mg x 14 tabs: EU/1/08/470/007; 150 mg x 56 tabs: EU/1/08/470/008; 200 mg x 56 tabs: EU/1/08/470/011; Syrup (15 mg/ml) x 200 ml: EU/1/08/470/014; Solution for Infusion (10 mg/ml) x 20 ml: EU/1/08/470/016. **NHS Cost:** 50 mg x 14 tabs: £10.81; 100 mg x 14 tabs: £21.62; 100 mg x 56 tabs: £86.50; 150 mg x 14 tabs: £32.44; 150 mg x 56 tabs: £129.74; 200 mg x 56 tabs: £144.16; Syrup (15 mg/ml) x 200 ml: £38.61; Solution for Infusion (10 mg/ml) x 20 ml: £29.70. **Marketing Authorisation Holder:** UCB Pharma SA, Allée de la Recherche 60, B-1070 Bruxelles, Belgium. **Further information is available from:** UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 01753 534655. Fax: 01753 536632. Email: medicalinformationuk@ucb.com. **Date of Revision:** 01/2010 (10VPE0010). Vimpat is a registered trademark. **References:** 1. Vimpat Summary of Product Characteristics, 2010. 2. Beyreuther BK et al. CNS Drug Rev 2007; 13(1): 21-42. 3. UCB Data on file. **Date of preparation:** June 2010. 10VPE0137



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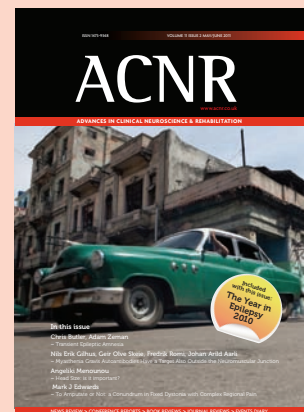
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Cover picture: Havana, Cuba, destination for Association of British Neurologists Joint Meeting with Neurology Section, Cuban Society of Neurology & Neurosurgery.

ACNR

Published by Whitehouse Publishing,
1 The Lynch, Mere, Wiltshire, BA12 6DQ.
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PRINTED BY

Buxton Press T. 01298 21 2000

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Transient Epileptic Amnesia



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For over 120 years it has been recognised that episodes of dense memory loss may be the sole presenting feature of epileptic seizures. Recent research suggests that 'transient epileptic amnesia' (TEA) should be thought of as a distinct neurological syndrome, with important implications both for clinical practice and for our scientific understanding of human memory.

TEA: development of the concept

In 1888, the renowned British neurologist John Hughlings Jackson described the case of Dr Z, a medical practitioner who suffered from an unusual variety of epilepsy.¹ During seizures, Z retained consciousness and was able to engage in complex, purposeful behaviour for which he was later amnesic. On one occasion, whilst at work, he experienced the onset of his typical epileptic aura. He subsequently examined, diagnosed and instigated treatment for a child with pneumonia, yet afterwards had no recollection of the consultation. Some years later, Z's brain came to autopsy, and a single, circumscribed lesion in the left uncus was discovered.²

The idea that transient, isolated memory loss may be the sole manifestation of epileptic seizures lay dormant in the scientific literature until the mid twentieth century, when debate began about the aetiology of the newly described syndrome of transient global amnesia (TGA). It is now clear that, in the majority of cases, TGA is not caused by seizure activity. However, Hodges and Warlow,³ despite using stringent diagnostic criteria, discovered that a significant minority (7%) of TGA patients they studied went on to develop complex partial seizures. These patients tended to have recurrent, briefer amnesic attacks than those with typical TGA.

The term 'transient epileptic amnesia' was coined in 1990 by Narinder Kapur⁴ in an essay in which he reviewed the published case reports, distilled the principal clinical features and concluded that TEA was a distinct neurological

Diagnostic criteria for TEA [5]

1. A history of recurrent witnessed episodes of transient amnesia
2. Cognitive functions other than memory judged to be intact during typical episodes by a reliable witness
3. Evidence for a diagnosis of epilepsy based on one or more of the following:
 - a. epileptiform abnormalities on electroencephalography
 - b. the concurrent onset of other clinical features of epilepsy (e.g. lip-smacking, olfactory hallucinations)
 - c. a clear-cut response to anticonvulsant therapy.

entity worthy of further study.

Using the diagnostic criteria of Zeman et al⁵ (see Box), we have recruited a cohort of over 50 patients with TEA from around the UK, as part of the wider TIME (The Impairment of Memory in Epilepsy) Project. This has enabled detailed study of the clinical, neuropsychological and radiological characteristics of this under-recognised and fascinating syndrome.^{6,7}

Clinical features of TEA

The amnesic attacks of TEA typically begin in late middle-age, the mean age of onset being 57 years. Males outnumber females by a ratio of two to one. As with most forms of epilepsy, the frequency of attacks is highly variable but, on average, they occur about once per month. A helpful clue to the diagnosis is that episodes of TEA characteristically occur upon waking, with around 70% of patients experiencing at least some attacks in this context.

During the amnesic episodes, patients are unable to remember recent events ('retrograde amnesia') and often cannot retain new informa-

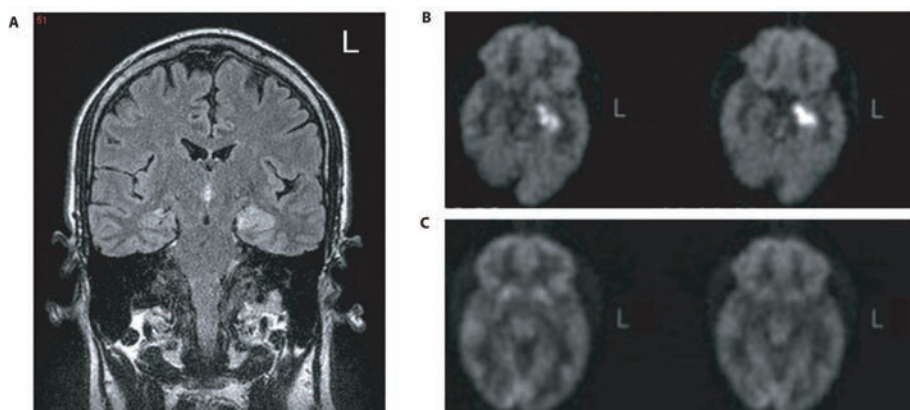


Figure 1: Radiological localisation of the seizure focus in TEA: (a) MRI scan showing high signal on T2-weighted imaging in the left medial temporal lobe of a patient with a flurry of attacks of TEA. (b) PET scan showing hypermetabolism in the left hippocampus at the time of the attacks, (c) with resolution after successful treatment 1 month later. (Reproduced from⁶).

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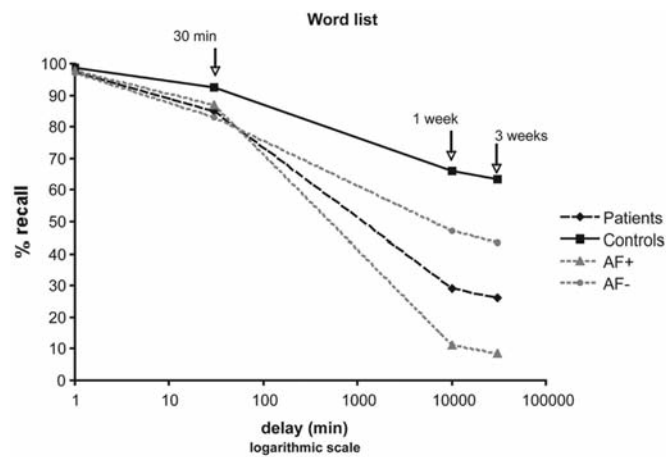


Figure 2: Accelerated long-term forgetting in a group of 24 patients with TEA, 12 of whom complained specifically of accelerated long-term forgetting (AF+), whereas 12 did not (AF-) (reproduced from⁶).

tion ('anterograde amnesia'). As a result, they may repetitively question their companions – "What day is it?", "What are we doing here?" Other cognitive faculties, such as perception, concentration, language and executive function, appear intact. We have encountered patients who have been able to play the piano, drive a car, translate from French to English or win a round of golf during amnesic episodes. The attacks typically last between 30 minutes and one hour, although much longer episodes are possible.

Whilst amnesia is the predominant feature of TEA attacks, careful enquiry can, in some instances, reveal other signs suggestive of epilepsy. The most common of these are hallucinations of smell or taste, experienced by up to 50% of patients with TEA. Subtle oral automatisms (lip smacking or chewing) or brief periods of unresponsiveness may also accompany some attacks. Interictal electroencephalography (EEG) reveals epileptiform abnormalities in only about one third of cases, although sensitivity may be significantly enhanced by sleep-deprivation. Magnetic resonance imaging (MRI) of the brain is usually clinically unremarkable. The amnesic attacks of TEA typically respond well to low dose monotherapy with an antiepileptic drug. However, treatment is often delayed as patients may be misdiagnosed as having TGA, 'psychogenic attacks' or dementia. Despite effective treatment of the amnesic episodes, 81% of patients with TEA complain of significant ongoing memory difficulties.⁶

Pathophysiology of TEA

Several features of TEA suggest that the medial temporal lobes (MTLs) are the seizure source. The MTL is critically involved in the laying down and retrieval of memories,⁸ as well as being a common site of seizure onset in temporal lobe epilepsy. The cognitive deficit in TEA attacks is characteristic of that observed with MTL dysfunction. Further anatomical clues are the high frequency of olfactory hallucinations and orolimentary automatisms, and the localisation of epileptiform activity, when it can be detected by EEG. Evidence obtained from EEG monitoring indicates that the amnesic spells of TEA can occur either as an ictal or a post-ictal phenomenon.⁹

When structural abnormalities are detected, they consistently impinge on the temporal lobes. A single case was studied at the time of a flurry of attacks: MRI scanning revealed high signal in the left hippocampus with hypermetabolism in the left hippocampus on peri-ictal PET which had resolved after successful treatment of his seizures (Figure 1).¹⁰ As a group, the 50 patients studied by Butler et al had mild but significant bilateral hippocampal atrophy.⁷

Neuropsychology of TEA

In most cases, general intellectual functioning is normal in patients with TEA. Indeed, the cohort of patients recruited to the TIME Project had an average mean full scale IQ of 118. This may reflect the difficulty of recognising TEA in the absence of an articulate description of its symptoms.

As mentioned above, complaints of interictal memory difficulties are common amongst patients with TEA. Nevertheless, patients are typically unimpaired on standard neuropsychological tests of memory.⁶ Instead, they describe problems that are invisible to these tests but have a significant impact on everyday life.

Remote memory impairment: 70% of patients with TEA report loss of memories for salient, personally experienced events from the remote past. For example, they may be unable to remember holidays they have been on or family weddings they have attended. A recent study confirms that there is a life-long depletion of autobiographical memories, particularly affecting the recollection of episodic details.¹¹ Memory for public events was also affected, but to a lesser degree and only for recent decades. A subgroup of patients also complains of difficulty in recognising familiar places and navigating along familiar routes.⁶

Accelerated long-term forgetting (ALF): 44% of patients describe the excessively rapid fading of newly acquired memories over a period of days to weeks. One patient was able to discuss the merits of a film he had seen with his daughter on the following day, but one week later had no recollection of the movie.¹⁰ Patients with TEA as a group show evidence of ALF on objective testing (Figure 2b). Those who specifically complain of the problem show especially severe long-term forgetting.⁶

The cause of remote memory impairment and ALF in TEA is unknown. They are not related to the volumes of MTL structures as measured on MR brain imaging⁷, but it is possible that they are due to more subtle structural damage yet to be detected. An alternative explanation is that they result from disturbance of normal brain function in the MTL, or elsewhere, by subclinical seizure activity. Reports of improvement of ALF upon treatment with antiepileptic medication are in keeping with this suggestion.^{12,13} Further research is clearly needed, particularly in the light of evidence that remote memory impairment and ALF also occur in the wider population of people with epilepsy.^{9,14}

Conclusion

Transient epileptic amnesia is a distinctive variety of temporal lobe epilepsy causing brief, recurrent, treatment-responsive attacks of transient amnesia, often on waking, generally in middle aged and elderly people. It is usually accompanied by interictal memory deficits including remote memory loss and accelerated long-term forgetting. ♦

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Presentation Rebif 8.8µg and 22µg: Pre-filled glass syringe containing 8.8µg or 22µg of Interferon beta-1a in respectively 0.2 or 0.5ml. Rebif 22µg or 44µg: Pre-filled glass syringe containing 22µg or 44µg Interferon beta-1a in 0.5ml. Rebif 8.8µg and 22µg: Disposable pre-filled pen injector (RebiDose) containing 8.8µg or 22µg of Interferon beta-1a in respectively 0.2 or 0.5ml. Rebif 22µg or 44µg: Disposable pre-filled pen injector (RebiDose) containing 22µg or 44µg Interferon beta-1a in 0.5ml. Rebif 8.8µg/0.1ml and Rebif 22µg/0.25ml: Pre-filled glass cartridge containing 132µg of Interferon beta-1a in 1.5ml. Rebif 22µg/0.5ml or Rebif 44µg/0.5ml: Pre-filled glass cartridge containing 66µg or 132µg of Interferon beta-1a in 1.5ml. **Indication** Treatment of relapsing multiple sclerosis. Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity. **Dosage and administration** Initiate under supervision of a physician experienced in the treatment of multiple sclerosis. Administer by subcutaneous injection. Recommended dose: Weeks 1 and 2: 8.8µg three times per week (TIW); weeks 3 and 4: 22µg TIW; week 5 onwards: 44µg TIW (22µg TIW if patients cannot tolerate

Date of Preparation: March 2011

higher dose). RebiDose pre-filled pen is for single use and should only be used following adequate training of the patient and/or carer. Follow the instructions provided in the package leaflet. Rebif solution for injection in cartridge is for multidose use and should only be used with the RebiSmart autoinjector device following adequate training of the patient and/or carer. Follow the instructions provided with the RebiSmart device. Limited published data suggest that the safety profile in adolescents aged 12–16 years receiving Rebif 22µg TIW is similar to that in adults. Do not use in patients under 12 years of age. Prior to injection and for 24h afterwards, an antipyretic analgesic is advised to decrease flu-like symptoms. Evaluate patients at least every second year of the treatment period. **Contraindications** History of hypersensitivity to natural or recombinant interferon beta, or to any of the excipients; treatment initiation in pregnancy; current severe depression and/or suicidal ideation. **Precautions** Inform patients of most common adverse reactions. Use with caution in patients with previous or current depressive disorders and those with antecedents of suicidal ideation. Advise patients to report immediately any symptoms of depression and/or suicidal ideation. Closely monitor patients exhibiting depression and treat appropriately. Consider cessation of therapy. Administer with caution in patients with a history of seizures and those receiving anti-epileptics, particularly if epilepsy is not adequately controlled. Closely monitor patients with cardiac disease for worsening of their condition during initiation of therapy. Patients should use an aseptic injection technique and rotate injection sites to minimise risk of injection site necrosis. If breaks in skin occur, patients should consult their doctor before continuing injections. If multiple lesions occur, discontinue Rebif until healed. Use with caution in patients with history of significant liver disease, active liver disease, alcohol abuse or increased serum ALT. Monitor serum ALT prior to the start of therapy, at months 1, 3 and 6 and periodically thereafter. Stop treatment if icterus or symptoms of liver dysfunction appear. Treatment has potential to cause severe liver injury including acute hepatic failure. Full haematological monitoring is recommended at months 1, 3 and 6 and periodically thereafter. All monitoring should be more frequent when initiating Rebif 44µg. New or worsening thyroid abnormalities may occur. Thyroid function testing is recommended at baseline and if abnormal every 6–12 months. Use with caution in, and closely monitor patients with, severe renal and hepatic failure or severe myelosuppression. Serum neutralising antibodies may develop and are associated with reduced efficacy. If a patient responds poorly and has neutralising antibodies, reassess treatment. Use with caution in patients receiving medicines with a narrow therapeutic index cleared by cytochrome P450. Women of childbearing potential should use effective

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contraception. Limited data suggest a possible increased risk of spontaneous abortion. During lactation, either discontinue Rebif or nursing. If overdose occurs, hospitalise patient and give supportive treatment. **Side effects** In the case of severe or persistent undesirable effects, consider temporarily lowering or interrupting dose. **Very common:** flu-like symptoms, injection site inflammation/reaction, headache, asymptomatic transaminase increase, neutropenia, lymphopenia, leucopenia, thrombocytopenia, anaemia. **Common:** injection site pain, myalgia, arthralgia, fatigue, rigors, fever, pruritus, rash, erythematous/maculo-papular rash, diarrhoea, vomiting, nausea, depression, insomnia, severe elevations of transaminase. **Serious side effects include:** injection site necrosis, hepatic failure, hepatitis with or without icterus, severe liver injury, anaphylactic reactions, angioedema, erythema multiforme, erythema multiforme-like skin reactions, seizures, thromboembolic events, thrombotic thrombocytopenic purpura/haemolytic uremic syndrome, suicide attempt, Stevens-Johnson syndrome, dyspnoea, retinal vascular disorders. Consult the Summary of Product Characteristics for more information relating to side effects. **Legal category POM. Price** Rebif 8.8µg and 22µg: 6 (0.2ml) + 6 (0.5ml) syringes – £552.19. Rebif 22µg: 12 syringes (0.5ml) – £624.77. Rebif 44µg: 12 syringes (0.5ml) – £813.21. Rebif 8.8µg and 22µg: 6 (0.2ml) + 6 (0.5ml) pens – £552.19. Rebif 22µg: 12 pens (0.5ml) – £624.77. Rebif 44µg: 12 pens (0.5ml) – £813.21. Rebif 8.8µg/0.1ml and 22µg/0.25ml: 2 cartridges – £406.61. Rebif 22µg/0.5ml: 4 cartridges – £624.77. Rebif 44µg/0.5ml: 4 cartridges – £813.21. For prices in Ireland, consult distributors Alphar Services Ltd. **Marketing Authorisation Holder and Numbers** Merck Serono Europe Ltd, 56 Marsh Wall, London, E14 9TP; EU/1/98/063/007; 003; 006; 017; 013; 016; 010; 008; 009. **For further information contact: UK:** Merck Serono Ltd, Bedford Cross, Stanwell Road, Feltham, Middlesex, TW14 8NX. Tel: 020 8818 7373. **Republic of Ireland:** Merck Serono, 4045 Kingswood Road, Citywest Business Campus, Dublin 24. Tel: 01 4687590. **Date of Preparation** July 2010.

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Myasthenia Gravis Autoantibodies Have a Target Also Outside the Neuromuscular Junction

Welcome to the first article in a series on leading Norwegian discoveries in neurology and neuroscience. All the selected discoveries have links to ongoing research projects in leading groups. They span clinical to more basic topics. The discoveries are all relevant for clinicians evaluating and treating patients with brain and nervous system disease. Neuroscience with a clinical focus has been a priority for Norwegian research. Further expansion is planned in cooperation between the universities, the university hospitals, the Research Council of Norway, and the Norwegian Brain Council. Although the discoveries in this series are presented as Norwegian, they all appear in an international context. They represent small pieces fitting into the bigger puzzle, but contribute to elucidating mechanisms for brain and neuromuscular function, thus laying foundations for improved treatment of human disease.

Myasthenia gravis (MG) was firmly established as an autoimmune disease in 1976.¹ The key factor leading to this conclusion was the detection of autoantibodies against acetylcholine receptors of the postsynaptic neuromuscular membrane. These antibodies had a direct symptom-inducing effect.² In 2001, it was shown that MG in a subgroup of patients was associated with autoantibodies to MuSK, a muscle-specific kinase in the post-synaptic membrane and functionally linked to the acetylcholine receptor.³ However, it had been known since 1960 that sera from MG patients contained autoantibodies against a mixture of skeletal muscle antigens.⁴

In 1992, we first published that the ryanodine receptor (RyR) in muscle is a target for MG autoantibodies.⁵ RyR represents the calcium release channels of sarcoplasmic reticulum in both skeletal and heart muscle (Figure 1). The identification of this antigen raised new questions about MG disease mechanisms, pathogenic antibody effects, and antibodies as markers for disease severity and treatment response.

Around the same time, our research group in co-operation with groups in USA and Germany found titin to be another antigen for autoantibodies in MG patient sera.^{6,7} Titin is a large intracellular protein that stretches through the entire sarcomere (Figure 2). It has elastic properties, and is important for muscle development and regeneration. The identification of RyR and titin antibodies in MG opened up a new field of research.

We had shown already in 1984 that MG-related muscle antibodies cross-react with

muscle-like epitopes in thymomas.⁸ By using specific, experimental muscle antibodies, transmembrane RyR epitopes were detected on human epithelial thymoma cells.⁹ Similarly titin epitopes were identified by another group on the same thymoma cells.¹⁰ Titin mRNA transcripts covering the main immunogenic region of the molecule were also shown to be present in MG thymomas.¹¹ Thus, the RyR and titin immune responses represented important elements in proving how thymomas can induce autoantibody production and MG.

RyR and titin autoantibodies mainly occur in thymoma-associated MG and late onset MG (MG onset > 50 years and thymus atrophy). Such antibodies hardly ever occur in early onset MG (MG onset < 50 years and thymus hyperplasia), ocular MG or MuSK-associated MG. RyR antibodies have a high specificity for the presence of a thymoma (>90%), but a much lower sensitivity (70%), whereas titin antibodies have a higher sensitivity (>90%), but a lower specificity (70%) for a thymoma.¹² This illustrates how analysis for titin and RyR antibodies in MG patients is of practical clinical value in diagnosing MG subtype, especially in determining if the presence of a thymoma is likely or unlikely. Microthymomas are difficult to identify correctly on MR and CT, whereas thymic hyperplasia on imaging can be mistaken for a thymoma. MG patients without a thymoma are grouped according to age of onset, local or generalised symptoms, thymus pathology, HLA genotype, but also according to autoantibody status. A distinction between the groups early onset MG and late onset MG is difficult with age-overlap between

groups, and there is a need for additional markers. The subgroups differ regarding prognosis and therapeutic response to specific interventions. Titin and RyR antibodies occurring in some but not all MG patients illustrate that MG pathogenesis is heterogeneous and that subgrouping is relevant. The presence of such autoantibodies strongly favours a thymoma or late onset MG. Presence of the autoantibodies is also associated with relevant genotypes.¹³

MG patients with titin and RyR antibodies respond less well to thymectomy than patients without such antibodies.¹² Especially in patients with no thymoma and MG symptom onset between 40 and 70 years of age, thymectomy or not represents a therapeutic dilemma. Thymus hyperplasia, severe generalised symptoms and lower age favour thymectomy. Absence of titin and RyR antibodies does the same, indicating that the patient pathogenetically belongs to the early onset MG subgroup even with a debut age > 40-50 years.

Whereas antibodies against acetylcholine receptor and MuSK bind to their muscle antigen *in vivo* and lead to a muscle weakness typical for MG, *in vivo* binding has not been shown for RyR and titin antibodies. These latter antigens are localised intracellularly. An access for circulating autoantibodies to intracellular antigens is still debated. These human MG antibodies have the potential to bind to the RyR channels, and they do so *in vitro*. The RyR becomes locked in a position closed for calcium transport after binding of antibodies from MG patients.¹⁴ MG patients with antibodies with a strong functional effect on RyR channels *in vitro* have more severe clinical symptoms. The immunosuppressive drug tacrolimus may have a symptomatic effect in MG patients with RyR antibodies through its effect on RyR-mediated calcium release.¹⁵

Titin and RyR antibodies are markers for a more severe MG disease, and more often with

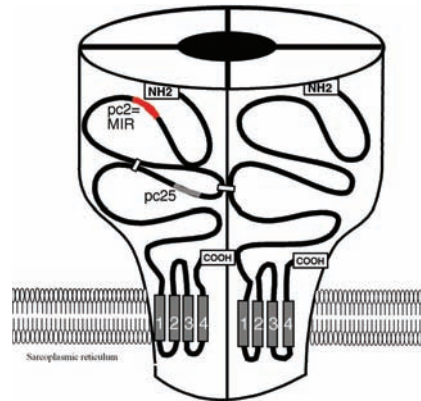


Figure 1: The ryanodine receptor (RyR) represents the calcium channel in the sarcoplasmic reticulum membrane. Most autoantibodies against RyR in MG patients are directed against the main immunogenic region (MIR), marked with red on the figure.

bulbar, neck and respiratory muscle involvement.¹⁶ MG patients have been reported with focal myositis, and also with cardiomyositis. The MG autoantibodies against titin and RyR react with the same antigens of skeletal and cardiac muscle. As the presence of titin and RyR autoantibodies is linked to a more severe disease, MG patients with such antibodies should probably receive more intense and longer lasting immunosuppressive drug therapy, even though treatment response has not been properly examined in MG subgroups defined according to antibody status.

MG is a heterogeneous disease characterised by autoantibodies to skeletal muscle. Autoantibodies against the muscle proteins RyR and titin can be used as specific and sensitive markers for thymoma MG and late onset MG. Furthermore such antibodies indicate a more severe MG, so that their presence usually makes long-time immunosuppressive therapy necessary. All aspects of MG are not easily explained by antibodies against acetylcholine receptors or MuSK alone. ♦

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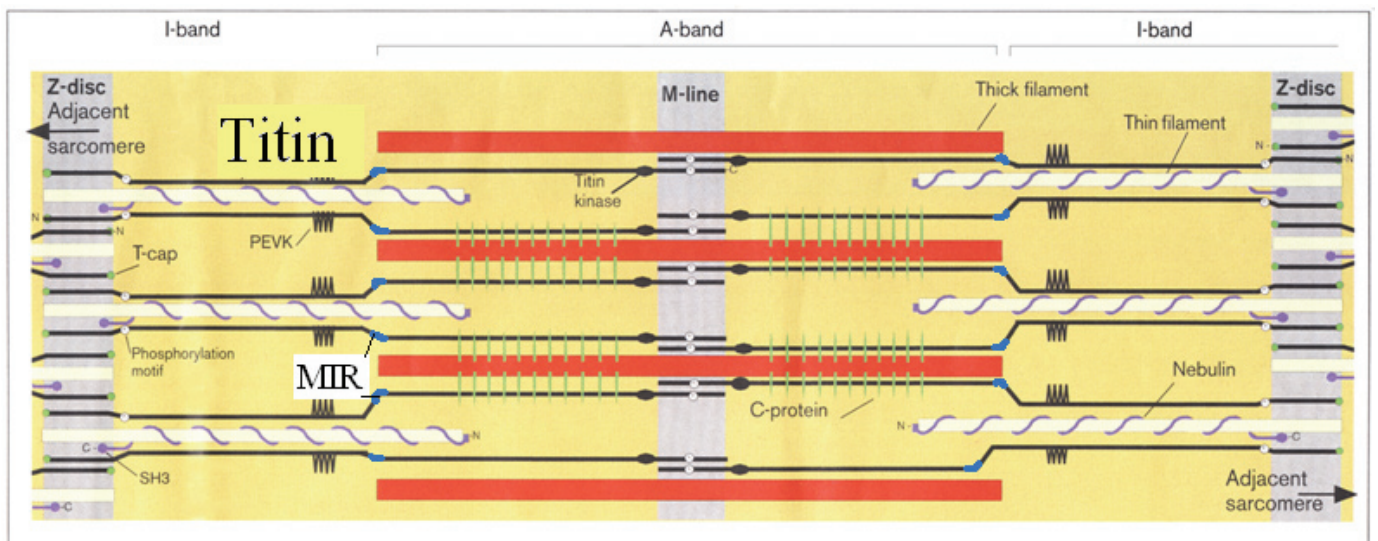


Figure 2: Titin stretches through the entire sarcomere. The protein is marked as a black line on this figure. Most autoantibodies against titin in MG patients are directed against the main immunogenic region (MIR).

Head Size: is it important?



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The assessment of growth in general and more particularly the measurement of the head circumference is an integral part of the Paediatric Neurological Examination. Very important clues can be revealed from the head size and shape which will guide the differential diagnosis and the need for further investigations. The head grows through to adulthood as is demonstrated in the head circumference charts (Figure 1 overleaf). It is also known from forensic studies that the timing of complete suture closure depends on the site of suture, the sex and the ethnic group, and the process continues till the age of 50.¹

Head size and cranial volume

In early infancy the skull bones are not fused together to allow for brain growth. The head grows rapidly antenatally and in the first three months. The rate of increase in head circumference is 3cm per month. The anterior fontanelle closes between 9-18 months. Between 4-6 years of age the head circumference increases by one cm per year.

The skull is filled with three compartments: brain, cerebrospinal fluid and blood. Expansion of one compartment is at the expense of another. The thickness of the skull bones also plays an important role in head size.

Head circumference (HC) is used as a surrogate measurement of brain size and brain growth

but it is only imperfectly correlated with brain volume. The head circumference is determined by measuring the greatest occipitofrontal circumference (from the occipital prominence to the frontal prominence – taking the biggest measurement of three). The accuracy of the measurement is influenced by the presence of fluid beneath the scalp i.e. oedema, blood, cephalohaematoma, and by the head shape. A round head has larger volume than an oval shaped head and a head with a relatively larger occipitofrontal circumference has a larger volume than a head with a relatively large biparietal diameter. Obviously measurements over time are more informative and should be plotted to the appropriate chart for sex and conceptional age.

Macrocephaly

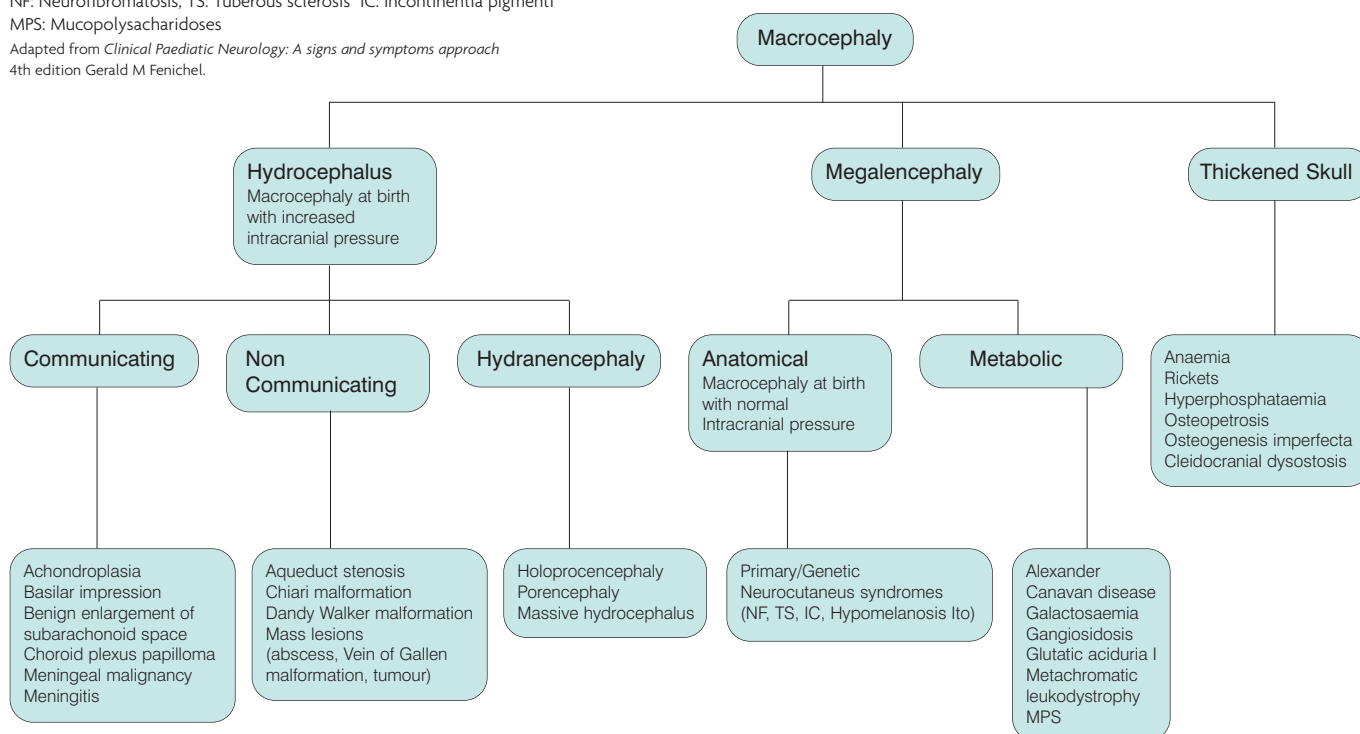
Macrocephaly denotes a large head which is larger than two standard deviations from the normal distribution. That means that 2% of the normal population is macrocephalic, often with a familial tendency. It is therefore essential to measure the HC of the parents before considering further investigations.

Causes of macrocephaly – Table 1

Macrocephaly can be due to hydrocephalus (increased CSF fluid), megalencephaly (enlarge-

Table 1: Causes of macrocephaly

NF: Neurofibromatosis, TS: Tuberous sclerosis IC: Incontinentia pigmenti
MPS: Mucopolysaccharidoses
Adapted from *Clinical Paediatric Neurology: A signs and symptoms approach*
4th edition Gerald M Fenichel.



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for allele HLA-B*1502 in individuals of Han Chinese and Thai origin as this has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome (SJS) when treated with carbamazepine. Examine serum sodium levels in patients with pre-existing renal disease or who are treated with medicinal products which may lead to hyponatraemia or if clinical signs of hyponatraemia occur. Discontinue if clinically relevant hyponatraemia develops. Do not use in primary generalised seizures. Prolongations in PR interval have been observed. Caution in patients with medical conditions or when taking concomitant medicinal products associated with PR prolongation. Monitor for signs of suicidal ideation and behaviours. **Drug interactions:** Has an inducing effect on the metabolism of medicinal products mainly eliminated by CYP3A4 or UDP-glucuronyl transferases, therefore the dose of these products may need to be increased when used concomitantly with Zebinix. May take 2 to 3 weeks to reach the new level of enzyme activity when initiating, discontinuing or changing dose, therefore take time delay into account when using with other medicines that require dose adjustment. Interactions can arise when co-administering high doses with medicinal products that are mainly metabolised by CYP2C19. Carbamazepine: Zebinix dose may need to be increased if used concomitantly with carbamazepine. Concomitant treatment with carbamazepine increased the risk of the diplopia, abnormal coordination and dizziness. An increase in other adverse reactions cannot be excluded. Phenytoin: An increase of Zebinix dose and a decrease of phenytoin dose may be required. Lamotrigine and topiramate: No dose adjustments are required. Valproate and levetiracetam: Concomitant administration appeared not to affect the exposure to eslicarbazepine but has not been verified by conventional interaction studies. Oral contraceptives: Interacts with the oral contraceptive. Simvastatin: An increase of the simvastatin dose may be required when used concomitantly with Zebinix. Warfarin: Can decrease exposure to S-warfarin. No effects on R-warfarin

or coagulation. Monitoring of INR should be performed in the first weeks after initiation or ending concomitant treatment. Digoxin: no effect. MAOIs: an interaction between eslicarbazepine acetate and MAOIs is theoretically possible. **Side effects:** Adverse reactions were usually mild to moderate in intensity and occurred predominantly during the first weeks of treatment with Zebinix. Refer to SPC for all side effects. Very common effects (≥1/10): dizziness, somnolence. Common effects (≥1/100, <1/10): Headache, abnormal coordination, disturbance in attention, tremor, diplopia, vision blurred, vertigo, nausea, vomiting, diarrhoea, rash, fatigue, gait disturbance. Serious side effects: hypersensitivity, hyponatraemia, dehydration, grand mal convulsion, ocular hyperaemia, palpitations, bradycardia, hypertension, hypotension, epistaxis, liver disorder, drug toxicity, poisoning. Some rare adverse reactions such as bone marrow depression, anaphylactic reactions, severe cutaneous reactions (e.g. Stevens-Johnson Syndrome), systemic lupus erythematosus or serious cardiac arrhythmias did not occur during clinical studies. However, they have been reported with oxcarbazepine and their occurrence during treatment with Zebinix cannot be excluded. **Legal category:** POM. **Basic UK NHS cost:** Zebinix 800 mg; pack of 30 £154.20. **Marketing authorisation numbers:** EU/1/09/514/012-020. **Marketing authorisation holder:** Bial-Portela & C^a, S.A. À Av. da Siderurgia Nacional 4745-457 S. Mamede do Coronado – Portugal. **Further information from:** Eisai Limited, European Knowledge Centre, Mosquito Way, Hatfield, Herts, AL10 9SN, UK. **Date of preparation:** December 2010

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ment of the brain) or thickening of the skull.
Investigations for macrocephaly – Table 2
 Start with a thorough history and examination. Previous measurements of the head circumference, the rate of growth and full developmental history are critical. Initial neuroimaging (preferably MRI) will guide the clinician for further investigations and management. If the cause is hydrocephalus referral to neurosurgery will be necessary. If other causes are suspected then a basic metabolic screening along with baseline biochemistry tests and possible referral to a clinical geneticist will be

Table 2: Investigations of Macrocephaly
<ul style="list-style-type: none"> • History • Examination including auscultation of the skull for bruit • Development • Rate of head growth – serial measurements • CT head/MRI head preferably • FBC • Urea/electrolytes • Bone profile • Thyroid function test • Plasma amino acids • Urine amino acids and organic acids, glycosaminoglycans

required.

Specific causes of macrocephaly

The Dandy Walker malformation consists of a triad of partial or complete agenesis of the cerebellar vermis, cystic dilatation of the posterior fossa communicating with the fourth ventricle, and hydrocephalus. The hydrocephalus may not be present at birth but develops later. In two thirds of cases other malformations are found, the commonest of which is agenesis of the corpus callosum. The presentation is with macrocephaly, occipital bulging and symptoms of posterior fossa compression such as apnoea, nystagmus, ataxia and brisk leg reflexes. MRI brain scan is the investigation of choice. The management is neurosurgical with decompression of the cyst and a ventriculoperitoneal (VP) shunt of the lateral ventricle and the posterior fossa cyst.

Benign enlargement of the subarachnoid space (also called external hydrocephalus, extra ventricular hydrocephalus and benign subdural effusions). This is a self limited disorder of unknown aetiology. A genetic cause is likely but not as yet identified. It is more common in males and a large head is the only feature. The anterior fontanelle is large but soft. Neurological examination, development and cognition are normal. Neuroimaging reveals an enlarged subarachnoid space, widening of the sylvian fissure and normal ventricular size. The latter distinguishes the condition from cerebral atrophy. These infants do not require any intervention or repeat scans after the diagnosis is established. They are reviewed clinically with monitoring of the

Table 3: Causes of microcephaly HIE: hypoxic ischaemic encephalopathy
 Adapted from *Clinical Paediatric Neurology: A signs and symptoms approach* 4th edition Gerald M Fenichel.

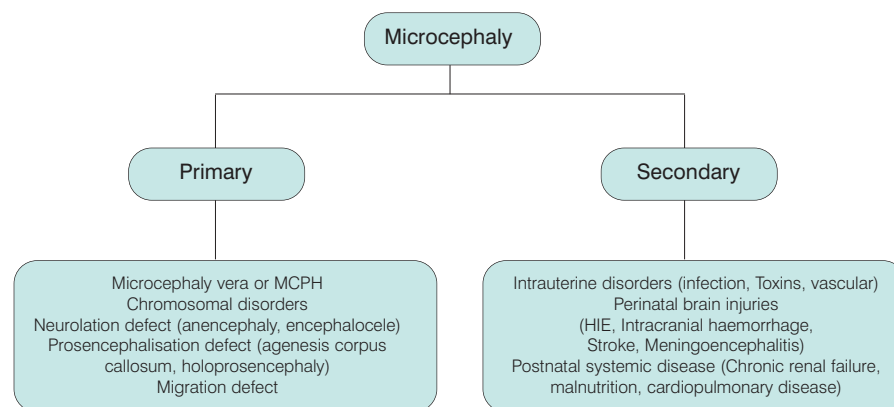
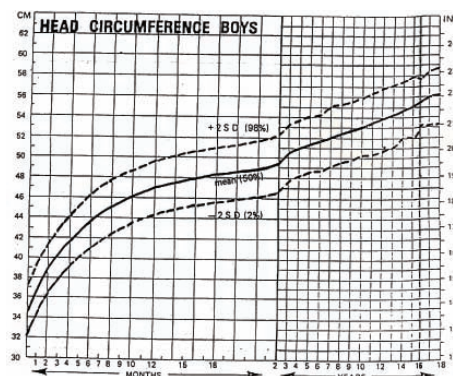


Figure 1



head circumference which should follow the 98th centile.

Microcephaly

Microcephaly means small head – less than 2SD below the mean for age and sex. It is important to note that there are also differences between different ethnic groups and that needs to be taken into account before a diagnosis is made. For example, in a study in Leicester it was found that Asian newborns had smaller head circumference than their Caucasian counterparts.⁷

It is important to investigate cases of microcephaly appropriately and identify the cause, as small head implies a small brain, reflecting poor brain growth. Most full term microcephalic infants represent the extreme end of the normal range. Those with normal neonatal neurological examination will be expected to have normal intelligence at the age of seven. A HC <3 SD at birth usually indicates later mental retardation and learning difficulties.

The causes of microcephaly (Table 3) can be divided into primary and secondary. Primary microcephaly includes conditions in which the brain is small having never formed properly due to genetic or chromosomal abnormalities. The head circumference is small from birth onwards with the exception of some chromosomal abnormalities in which the HC may be normal at birth.

In secondary microcephaly the growth of a normal forming brain is impaired by an

acquired disease process. In these conditions the HC may be normal at birth but the head fails to grow thereafter. Due to the lack of brain growth the force keeping the cranial bones separated does not exist and there may be early closure of the sutures or even overlapping of the skull bones. In these cases the skull shape is normal and the intracranial pressure is not increased. These features distinguish primary microcephaly from craniosynostosis.

Investigation of microcephaly

- History (perinatal – family history)
- Examination – dysmorphic features – malformations
- Development
- Growth – serial measurements of HC
- MRI brain
- Baseline biochemistry, metabolic screen
- Genetic testing – karyotype, molecular genetics
- TORCH screen
- Ophthalmology

MRI brain scan is very informative in distinguishing primary from secondary microcephaly. In the majority of cases the scan would be either normal or abnormal with developmental cerebral malformations (migration, prosencephalisation or neurolation defects). In secondary microcephaly cases there will be evidence of brain atrophy, porencephaly and ventricular enlargement. If primary causes are suspected a referral to the clinical geneticist is required to identify potential chromosomal or genetic abnormalities. Congenital infection screening and basic biochemical and metabolic investigation may be required.

Autosomal recessive primary microcephaly (MCPH)⁴

MCPH is a neurodevelopmental disorder with three defining clinical features:

- A. Congenital microcephaly at least 4 SD below mean for age and sex
- B. Mental retardation which is non progressive and no other neurological findings such as spasticity or seizures are seen. Even though seizures are very rare their presence does not exclude the diagnosis, and
- C. Normal height, weight, appearance and



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The head size, the growth rate and the shape of the head are important pointers towards benign or more sinister medical conditions

results on chromosome analysis and brain scan.

MCPH is a disorder of foetal brain growth with the cerebral cortex showing the greatest reduction in volume. All data suggest that MCPH is a primary disorder of neurogenic mitosis and not of neuronal migration. All four known genes are expressed in the neuroepithelium and the phenotypic features and brain scans suggest that the MCPH patient has a small brain that functions normally for its size. Patients with a MCPH1 gene mutation may have reduction in height or may have periventricular heterotopias pointing to a more specific phenotypic – genotypic correlation.

There are at least seven MCPH loci and four genes have been identified: MCPH 1 encoding Microcephalin, MCPH encoding CDK5RAP2 (Cyclin Dependent Kinase 5 Regulatory Associated Protein 2) MCPH 5 encoding ASPM (Abnormal Spindle-like Microcephaly Associated) and MVPH 6 encoding CENPJ (Centromere Associated Protein)

From antenatal scans we know that head size is normal up to week 20 whereas a decreased HC is seen by week 32. At birth the HC is 4-12 SD below mean without variations after that. The cerebral cortical gyral pattern is simplified with slight reduction of white matter volume but the architecture of the CNS is normal without evidence of a neuronal migration defect.

Interestingly, patients with MCPH have mild to moderate mental retardation and the early milestones are achieved at expected times. Later motor and social milestones are mildly delayed with speech development consistently delayed. They have good fine motor skills and balance as young adults and they do well in sports. Their affect is 'happy' and they can follow instructions and learn living skills.

The mode of inheritance is autosomal recessive and the incidence is higher in Asian and Arab populations where consanguineous marriage is practised. Prenatal diagnosis and carrier testing are becoming increasingly available.

Conclusion

Head size, growth rate and the shape of the head are important pointers towards benign or more sinister medical conditions. A detailed history, thorough examination, including developmental assessment and serial HC measurements, will give the clinician important clues for the differential diagnosis. The measurement of HC of the parents and the siblings in combination with appropriate neuroimaging will further assist in the diagnosis and ongoing management. Expert assessment by a clinical geneticist is essential as our understanding of the genetic causes of these conditions improves. ♦

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Neurological Literature: Headache (Part 8)

The Master and Margarita, the posthumously published masterpiece of the Russian author Mikhail Bulgakov (1891-1940), depicts Pontius Pilate as suffering from "the invincible, terrible illness ... hemicrania, when half of the head aches ... there's no remedy for it, no escape ... I'll try not to move my head". Thus afflicted, Pilate interrogates the prisoner, Yeshua Ha-Nozri, who assures him "your suffering will soon be over, your headache will go away", but "a dull, slightly aching reminder of the morning's infernal pain" still lingers later in the day following the execution of the prisoner. Other characters in the novel are also affected, or nearly so, with headaches: Margarita has an ache like a needle in her temple all evening; Woland almost has a migraine from the roaring in the bar; and both the Master and Margarita have a slight ache in the left temple following Satan's ball.¹ Zayas has argued that Pilate's hemicrania reflects Bulgakov's personal experience of migraine, based on the evidence of his diaries.² Since Bulgakov was a qualified doctor, it might also be reasonably assumed that he encountered headache in practice, some corroboration for which may be found in his semi-fictional accounts published as *A Country Doctor's Notebook*. In *Black as Egypt's Night*, a miller from Dultsevo reports to young Dr Bulgakov that "Every day at twelve o'clock my head starts to ache, then I seem to get hot all over .. It makes me shiver for a couple of hours or so and then it goes", leading the doctor to diagnose malaria. In *Morphine*, an account of morphine addiction, an "absurd, hysterical letter" from the addict provokes a migraine in the recipient (Bulgakov).³

Another Bulgakov, Valentin Fedorovich (1886-1966), acted as secretary to Leo Tolstoy (1828-1910) in the last year of the novelist's life, and subsequently published his diary for that year, which in turn became the starting point for Jay Parini's novel *The Last Station*, the motion picture of which was strangely neglected by mainstream cinemas in 2010. The story is told from several viewpoints, including that of Tolstoy's wife, Sofya Andreyevna, who at several points reports herself afflicted with headache, e.g.:

*I've been lying in bed with a headache, watching the snow fall, drinking tea. I cannot read. My head is tight as a drum, pounding. And I do not have the gramophone in my bedroom.*⁴

Parini's novel is based on the diaries kept by those in Tolstoy's inner circle. The edited diary of Sofia Tolstoy, covering the period 1862 to 1919,⁵ attests not only to her headaches, but also to those of Tolstoy himself, and other family members, including their youngest daughter, Sasha (born 1884):

21st June 1897. Sasha ... was looking very pale and said she felt sick and had a headache. ... Then she vomited and had to lie down. She often gets migraines, like her father.

Reading the diaries, I cannot escape the conclusion that Sofia's portrayal in the film of *The Last Station* is not entirely fair. Indeed, some might gauge that her character has been impudently traduced, or, at the

very least, that she was perhaps more sinned against than sinning. However, the tradition of cinematic misrepresentation of Tolstoy's last days is a long one, dating to 1912 (*The Flight of a Great Old Man*, described by Sofia as a lampoon of her), and at least *The Last Station* secured for Helen Mirren an (obligatory?) Oscar nomination for her portrayal of Sofia. Parenthetically, one may note that two figures in the history of neurology appear transiently, as offstage figures, in Sofia Tolstoy's diary. Kozhevnikov, later credited with the earliest description of what has come to be known as Rasmussen's encephalitis,⁶ was apparently consulted by Tolstoy's son Lyova in 1895; and on 24th November 1900 Tolstoy "went to a musical evening at the lunatic asylum", namely the psychiatric clinic of Professor SS Korsakov.

Chekhov was one of Leo Tolstoy's many occasional visitors, both at Yasnaya Polyana and in Yalta. Previous examples of headache in Chekhov's plays have been cited,⁷ and they may also be found in some of his short stories.⁸ For example, in *Peasants*, Kiryak has "a terrible hangover ... shaking his splitting head". In *The Bishop*, Bishop Peter "had the same headache as yesterday ..", and later "he had a splitting headache". This is one symptom of a febrile illness which is eventually diagnosed as typhoid.

Whilst headache is an incidental finding in all the aforementioned works, occasional pieces proclaim this to be their subject matter: one thinks of Robert Herrick's 1648 poem *The Head-ake*.⁹ Another example is the short story entitled *Migraine* by Tobias Wolff, from the collection *The Night in Question*. The story begins:

It began while she was at work.

(Although the nature of this work is not made explicit, the fact that she, Joyce, works at a keyboard, with lab reports, and with cubicles around her from which the "steady click of other keyboards" is heard, suggests the possibility of a medical secretary.) It transpires that this headache is occurring in the context of a relationship which is breaking up. At home Joyce tries herbal tea, which "helped. Not much, really ...", and kneading her temples, and she has apparently tried other remedies in the past including getting drunk and stoned, but it is head massages from her (soon to depart) partner which help most. Her symptoms include dizziness and:

... at the worst moment she went suddenly deaf, as if someone had pushed her head underwater ...

a symptom which recurs again later. Of note, headache also crops up in another of Wolff's stories, *Flyboys*:

... handsome families ... it was clear, did not ... come down with migraines.

*The sound grew larger and louder and emptier, the sound of emptiness itself, emptiness throbbing like a headache.*¹⁰ ♦

Series Editor



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Welcome to the sixth in a series of articles in *ACNR* exploring clinical dilemmas in neuropsychiatry. In this series of articles we have asked neurologists and psychiatrists working at the interface of those two specialties to write short

pieces in response to everyday case-based clinical dilemmas. We have asked the authors to use evidence but were also interested in their own personal views on topics. We would welcome feedback on these articles, particularly from readers with an alternative viewpoint.



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To Amputate or Not: a Conundrum in Fixed Dystonia with Complex Regional Pain

Case

Dear Neurologist,

Many thanks for seeing this 38-year-old woman with a fixed abnormal posture of the right hand and arm that began 12 years ago after she sprained her wrist in what seemed to be a simple injury. She has been extensively investigated and no cause has been found. She is in severe pain and nothing has helped. She has been to see an orthopaedic surgeon who has suggested he could amputate the limb above the elbow, and she is seriously considering this option. What would your advice to her be?

Limb injury, particularly minor injury that does not cause nerve damage, is very common. Such injuries usually cause no more than minor annoyance, but in a small group of people such injuries trigger severe disabling symptoms which are difficult to understand pathophysiologically, and are (perhaps because of this) difficult to treat. Some patients develop severe pain as a dominant symptom which may spread outside the original site of injury and is similar in character to neuropathic pain. Change in temperature of the limb, swelling, abnormal hair and nail growth can all occur, and movement of the limb is often limited. In the setting of normal investigations, this is the picture of complex regional pain syndrome type 1 (CRPS1). Other patients have both pain and fixed abnormal postures of the limb. These postures share some features with dystonia, but lack many important features of typical dystonia. This is the picture of fixed dystonia. It seems increasingly likely that CRPS1 and fixed dystonia occupy points on a spectrum of the same disorder.¹

With this background in mind, let's return to the problem in the referral letter. My approach to this scenario would be to address three main aspects:

1. Am I happy that this case fits within the category of fixed dystonia?
2. What therapies have been explored already and what options might there be?
3. What am I going to advise the patient and GP about amputation?

Is this fixed dystonia?

Typical dystonia is mobile: the affected body part may well have a "preferred" posture, for example a head turn to the right in a patient with cervical dystonia. However the posture is usually not fixed, and movement against the main direction of the posture is still possible. Many patients will have a sensory 'geste', where touching the affected body part will improve the posture. Typical primary dystonia has a clear distribution related to age at onset. While primary dystonia coming on in childhood often affects the whole body (but spares the face), adults usually get head and neck dystonia or task specific dystonia affecting the arms. Typical dystonia can be painful (in particular neck dystonia), but pain is not usually a dominant clinical feature. Response to botulinum toxin injections if given correctly is usually good. Fixed dystonia tends to violate most of these rules,¹ occurring in adults in the hand (in a non-task specific manner) or feet with fixed painful postures that are not improved by a sensory geste and are said not to respond to botulinum toxin (but see below). Of course, like all rules there are exceptions and fixed abnormal postures are seen in certain organic situations e.g. corticobasal degeneration, basal ganglia lesions, rare metabolic disorders such as Wilson's disease, aminoacidaemias and leucodystrophies. However excluding such conditions is often straightforward with history and examination and if necessary imaging and blood tests. I would occasionally

request nerve conduction studies of the affected limb to exclude any possibility of nerve injury that might have occurred at the time of the original trauma. Small fibre neuropathy is often suggested as a possible source of the pain in fixed dystonia/CRPS1², but there are a number of arguments to suggest this is unlikely to be the case,³ and I would not generally request thermal thresholds. So, with normal imaging, blood tests and nerve conduction studies combined with a typical history of minor injury followed swiftly by severe pain and fixed posture, I would feel fairly comfortable with the diagnosis of fixed dystonia. What I would want to find on examination would be a fixed postured limb with (paradoxically) little activation of muscles at rest despite the posture (if you feel the limb gently the muscles are often relaxed when no attempt is being made to alter the posture), but with clear resistance to passive movement of the limb. There is usually little or no voluntary movement possible, and muscles opposing the posture tend not even to be activated by the patient when requested to do so: this is very different from typical dystonia. Other signs are often present, for example a co-contraction type tremor, give way weakness. Additional history taking may reveal a history of other functional symptoms including non-epileptic attacks, weakness, sensory loss and fatigue.

What has been tried already, and are there other therapies available?

Conflict continues to rage in the movement disorder world as to the aetiology of this disorder. There is a somewhat unhelpful dualistic battle between those who feel this is an organic condition and those who would prefer to call it psychogenic. Both are probably right, and certainly the argument does little to help patients. On the organic side there is evidence of abnormal reflex sensitivity,⁴ cortical excitability⁴ and the occurrence of contractures in some patients, indicating the maintenance of postures even when unobserved. On the psychogenic side there is evidence of high rates of affective and dissociative symptoms in patients,¹ response to a multidisciplinary intervention based on psychotherapy,¹ clear dramatic placebo response in some patients⁵ and the common co-occurrence of more widely accepted functional disorders such as non epileptic seizures.¹ Not surprisingly there is a similar battle regarding the pathophysiology of CRPS1³.

The literature suggests a bleak therapeutic picture for those with fixed dystonia.¹⁶ For example in one follow-up study, 77% of patients were either the same or worse after a mean follow-up of 7.6 years.⁶ However, this need not necessarily be the case. Simply being honest with the patient regarding the disorder is of great importance. Often patients are relieved to hear that they have a problem that is 'recognised' rather than constantly being told how unusual they are. I would typically try to put forward a holistic model to the patient that encompasses the role of the injury in sensitising

the motor and sensory system, the deleterious effect of simply maintaining a posture for a long time (giving the example of limb immobilisation for fractures where quite severe pain, poor motor control and feelings of 'disconnection' from the limb are common), and the role of emotions in creating vulnerability to the effects of the initial injury and an abnormal attentional focus on the limb maintaining symptoms. Contrary to expectations, discussion in a sensitive way of the role of psychological factors in triggering and maintaining symptoms in this way can be met with understanding and acceptance. This can be helped by collaboration with a good pain team where a structured pain control program will usually include a significant amount of cognitive work which often spills over into helpful improvements in the abnormal posture. The key therapeutic aims would be to desensitise the limb, get it moving even if only passively at first, and to use psychological techniques to remove focus on symptoms, block out pain and explore, if the patient is willing, any longer term psychological issues. This rehabilitation approach is good in theory, but it requires a lot of collaboration between different teams which is difficult in many settings. Recently, botulinum toxin injections given following an explanation of the pathophysiology as above have been shown to produce a dramatic immediate effect,⁵ which, given that botulinum toxin takes days to start working, is clearly a placebo effect. Long term benefits and pitfalls of this approach are not certain, but in some patients I have found this a useful way to get the limb moving and to make subsequent physiotherapy more effective. Examination under anaesthetic can also have a role in convincing you and the patient that there are no significant contractures (as rarely these can occur). Videotaping this procedure and showing it to the patient afterwards can help bring home the fact that the limb can move out of its fixed position. In the right hands, a reaction may also occasionally be worth trying, particularly to rescue an otherwise desperate situation. One centre suggests intrathecal baclofen for such patients, but in my mind it is still uncertain whether sufficient blinding of the therapy occurred to cover for the possibility of a placebo effect in the published placebo controlled trial.⁷

What am I going to advise about amputation?

Whatever one's views on aetiology, it is clear that fixed dystonia is a potentially treatable, even completely reversible, disorder. In view of this, an irreversible invasive procedure such as amputation seems unadvisable. But what is the evidence?

It is surprisingly unusual (at least in terms of published reports) for patients with organic neurological disorders causing abnormal limb postures and/or pain to request amputation.⁸ In contrast, there is quite a large literature on amputation for CRPS1 with at least 70 cases reported.^{8,9} The descriptions of patients in these reports indicate that it is likely that some had

additional fixed dystonia. Recently a case series of five patients with fixed dystonia who sought or achieved amputation has also been published.⁸ The clear and unequivocal message from these reports is that amputation in the setting of CRPS1 with or without fixed dystonia carries a very high risk of causing harm to the patient. For example, in the largest case series of 34 patients with CRPS1 and amputation,⁹ 40% had periprocedural complications and 85% developed phantom limb pain. Only two cases reported benefit in pain reduction. Of the three cases of fixed dystonia reported by myself and colleagues who had achieved amputation,⁸ two developed phantom limb pain and the other developed fixed dystonia in the un-amputated arm and is now requesting a further amputation. From a pathophysiological point of view it is of interest that this group of patients appears more willing to seek amputation than patients with other causes of limb posture and pain. There might even be similarities to those with body integrity identity disorder – people with normal limbs who seek amputation.⁸ But leaving aside such speculation, the clear advice to the GP and patient in this case would be to avoid amputation at all costs. This is a problem with its origin in the brain, and amputating a limb is not going to alter that. In fact I would go so far as to say that on the current evidence, such a procedure would be unethical, as the chance of benefit is so low and the chance of significant harm so high. ♦

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Not My Usual Autopilot: Teaching during a complex-partial seizure



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Many of us know the experience of being in the middle of an activity that requires focus and attention to detail, but because the activity is one we perform on a routine basis and feels like second nature, we allow our minds to wander. We do not get alarmed if we realize we've missed our usual exit on our drive home on the interstate. Mildly ashamed at having lost our 'autopilot' sensors, we backtrack, re-enter the next on-ramp, and are home a few minutes behind schedule. Not a problem.

Seizure in the lecture hall

But what if one is lecturing to a packed university classroom, going through the same lecture she's presented semester after semester, only to notice from the podium that students look at you with alarmed expressions on their faces, that some signal to each other in hushed tones, while others sit frozen?

It happened to me exactly like that in early 1991. I was lecturing undergraduates at a major university, feeling totally secure since I'd been through the routine so many times before. This time, something was different. Why the puzzled looks, the whispers, the furtive glances between students? Maybe I've talked over their heads this time. Not to worry, I assured myself. I've always enjoyed good relations with my students.

Alas, I'd experienced a complex-partial seizure in the middle of a lecture. When I examined the end-of-semester student evaluations, I learned the details of what had occurred. Students reported that I'd been lecturing as usual. Then, I began to stare and mumble incoherencies. The class initially thought I was acting out the scene under discussion. I stood motionless, spoke inaudibly, and fiddled with my pen. A few students reported alarm at my sudden change of demeanor. Then, just as abruptly, within a few minutes I re-established composure

and continued exactly where I left off before the seizure began. These evaluations sealed my fate.

How would I have known that anything untoward had happened? I was utterly amnesic of the event. Although I later sensed that something was amiss, I dismissed those qualms. Since none of the students said anything about the episode after class, I finished the semester believing that my contract would be renewed for the following fall.

Loss of employment and denial

My confidence fell apart when I was summoned to the Dean's office at semester's end and was told that my sections for the fall semester had been closed. The explanations were vague and misleading. I was now out of a job. I chalked the issue up to departmental downsizing, that I was another lecturer let go to ease the university's financial squeeze.

Not so strangely, I never inquired about why I was dismissed from a promising career. Although persons with epilepsy are unconscious during their seizures, they develop a tendency to cocoon themselves and shun any discussion about their seizures. Denial explains why so many families and sufferers avoid facing details that may be crucial in understanding their condition and to prompt them to seek treatments beyond pharmaceuticals.

Delaying an investigation of one's epilepsy highlights the need to raise awareness about how damaging epilepsy can be. We now talk about sports-related concussions and the dangers they present; yet we maintain a veil of silence about the life-threatening perils of inadequately treated epilepsy. Public awareness that epilepsy surgery offers positive outcomes is vital in bringing about higher cures. With surgery, those suffering from intractable epilepsy immediately experience an improved sense of psychological wellbeing and are much better equipped to cope with the disease. Successful epilepsy surgery extends one's life expectancy.

Early seizures and accidents

When I was 18 years old, I had viral meningitis that included several grand mal seizures. After a week in hospital in 1966, the virus dissipated on its own. Doctors at the time concluded that there would be no long-term effects. In 1981, the seizures started again. They were mild and infrequent. Despite this, I completed my doctorate five years later in English literature at age 38 and embarked on a Post-doctoral Fellowship. I began

*Epilepsy surgery
restored my ability to
teach again,
completely seizure-free*

the usual lecture circuit and round of publications. During this period, not only did I have the seizure at the podium, but I also totaled my car by having a seizure while driving. On another occasion I experienced a seizure while frying fish; I immersed my hand in the searing oil and sustained third degree burns. Other accidents followed, such as one at age 50 when I walked into taxi lanes at a busy airport. I have no memory of any of these events other than the physical wounds that were quickly made apparent and required immediate medical treatment.

Damaged wire metaphor

How do seizures disrupt the brain's functions and cause damage? Picture an area of the brain as a bundle of intertwined telephone wires. Observe that a disruption has damaged the insulation on some of the wires. Over time they will touch each other, spark, and cause progressively more damage. The sound over the telephone becomes static. With the passage of time the static becomes more frequent, and the sound loses some of its clarity. An examination of the bundled cables reveals scorched wires and burned insulation. With careful mapping from the ends of the cables, the damaged wires can be identified, and with further investigation the remaining good cables can be located. If the defective wires are cut out, the remaining cables can continue to carry the signal. The static stops and the telephone can operate properly again. Just so with epilepsy surgery.

Amygdalohippocampectomy

In 2001, I had brain surgery at age 53 after having first undergone extensive brain mapping and a hospital investigation with closed-circuit television to pinpoint the locus of the seizures. The paroxysms were found to originate in the amygdalohippocampal complex. A scar was located on my right amygdala, and it, together with the damaged areas in the adjacent hippocampus, was removed. I have been completely seizure free since then. I resumed teaching in 2009.

Erasing prejudice

Discrimination towards those suffering from epilepsy is not new. To what extent is social exclusion related to our uneasiness about the unknown? Our culture also tends to devalue the experiences of the disabled. Although it is unlikely that someone would choose to have a condition that interrupts consciousness without warning, the testimonies of persons with improved epilepsy can be persuasive in raising public awareness of the condition. Surgical intervention has restored my ability to work. It ended the tortuous shame of having seizures in public. I hope that my story will prompt others whose seizures are uncontrolled to consider surgery as an option with a positive outcome. ♦

Sleep disorders from the Cleveland Clinic. A case a week

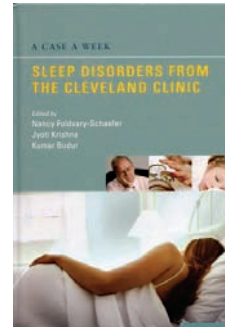
Compared to its position in the UK, sleep medicine in the USA is, as they say, a different "ball game". For example, an average American city will have approximately four times as many full polysomnography beds as exist in the whole of the British Isles. One might conclude that this disparity arises because, in the USA, there is a heightened awareness of poor quality sleep and its potentially deleterious effects on brain, mind, body and soul. There may

also be an appreciation of how virtually every neurological disorder may be adversely affected by a poor sleep-wake cycle – after all, "Sleep is by the brain, of the brain and for the brain" as one commentator famously opined. As an aside, in my general neurological practice, given my (un)natural bias, with the possible exception of distal myopathies and other minutiae, I usually have little difficulty in turning around any consultation to sleep-related matters.

In reality, the major differences almost certainly reflect the fact that sleep medicine is potentially "big business" with consequent diametrically opposite effects on public and largely privately funded health systems. With regards to levels of unsatisfactory nocturnal sleep or, indeed, wakefulness, one might also highlight the incidence of obesity in the USA but also the work ethic, whether reflected by the higher prevalence of shift work or the lack of "down time", compared to European standards.

In any event, it was with some trepidation that I approached this new book on sleep medicine, fearing that its extensive accounts of real life sleep-disordered patients from the well respected and noted Cleveland Clinic would have, at best, little relevance to my practice or, at worst, induce intense envy of the American system.

I needn't have worried; actually, I think this is an extremely readable, entertaining, useful and instructive book. Moreover, it left me feeling that, within reason and without much in the way of "kit", our approach, management and quality of care of such



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patients is, reassuringly, broadly similar in the UK.

If you are both interested in sleep and have a short attention span, this book should appeal. It is divided into 52 brief bite-size case reports, written by an impressively wide-ranging authorship, covering the whole spectrum of sleep disorders in 400 pages. The cases appear real, are often complex or "grey" and are portrayed in a refreshingly relaxed and humane style, warts and all. There is a degree of repetition, especially in the sections on insomnia

and breathing-related sleep disorders, which might not appeal particularly to the average UK neurologist. However, reading the accounts of how different experts approach similar problems was, for me at least, insightful and interesting. I certainly learnt a few things, such as how Prozac appears to enhance random eye movements which may mimic REM sleep ('Prozac eyes') in sleep investigations.

Not surprisingly, given the authorship, there is considerable emphasis on the International Classification of Sleep Disorders (ICSD, 2nd Edition). Arguably, this leads to a rather rigid and protocol-centred approach to many of the cases with a slavish reliance on investigation results rather than clinical impression. Another minor niggle was the practice of having short bibliographies at the end of each case when specific references would often have been more useful. Overall, however, there was little to fault. The amount of information packed into these case reports was impressive and the accompanying videos, available on-line, were reasonably helpful, if not of the highest quality.

Although I would argue that every neurologist and neuroscientist should be interested in sleep medicine, I am not entirely sure whether the impressive detail in this book would have general appeal. At the very least, though, it is accessible and generously illustrates the fascinating spectrum of symptoms and problems seen in a specialised sleep clinic. Whether a useful guide for dipping into or simply a cure for insomnia, it represents good value (around £30) and is thoroughly recommended. ♦

Editors: N Foldvary-Schaefer, J Krishna, K Budar. Published by: Oxford University Press (2011).

ISBN: 978-0-19-537772-9. Price: £32.50.

Pediatric Neurology. What Do I Do Now?

As a paediatric registrar hoping to pursue a career in paediatric neurology, I was very keen to review this book. One of the best pieces of advice I've been given as a junior doctor is that reading about interesting cases you encounter is the best way to learn, so I was very excited when I had an opportunity to read a book which is based on paediatric neurology case discussions. The author is an eminent American paediatric neurologist with a research interest in epilepsy. He compares reading his book "to wine tasting, where one can sample wine in small aliquots". And indeed, the reader has a brief taste of a variety of cases in paediatric neurology.

There are 28 chapters, which cover the more common conditions in paediatric neurology, including childhood absence epilepsy and febrile convulsions, as well as less common conditions like Hashimoto's encephalopathy and nonketotic hyperglycaemia. Each chapter starts with a case illustration, one of the book's strengths, since these are vivid and very realistic. They contain detailed descriptions of the presenting episode, past medical history and examination findings – all the information needed to answer the key question, 'What do I do now?'.

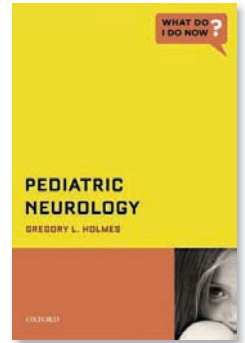
The subsequent discussion gives an overview of the condition with a practical guide to further investigation and management. I particularly liked the continuity between the case illustration and further discussion, which remains focused on the case. It reminds us, as clinicians, that every child we look after is an individual and that our approach should be tailored to that child's needs. Within the chapters there are useful tables (containing key points to remember and differential diagnoses), EEG examples and excellent MR images. The reader is given a list of references to key papers at the end of each chapter.

The case discussions varied, however, in quality and usefulness. The chapter on Rett's syndrome gives an excellent summary of the clinical stages of the disorder; there are useful notes on diagnostic criteria

and genetic testing for Rett's syndrome. The chapter on infantile spasms starts with a case illustration of a child with tuberous sclerosis, who develops infantile spasms. This is clearly taken from a real life as it shows the common pitfalls and difficulties in making the diagnosis. It is precise and to the point. Another of my favourite chapters was devoted to dopamine responsive dystonia, a condition not often seen in paediatric neurology. Having just come across a child with dystonia on the ward, I was keen to see what this book has to offer. I was not disappointed. The information was concise and the key features in the condition and its further management were highlighted.

The chapter on benign childhood epilepsy with centrotemporal spikes (BECTS), by contrast, was less useful for the UK reader: phenobarbital and phenytoin are said to be the drugs of choice, followed by carbamazepine and valproic acid (this reflects local American practice). There is an error in the same chapter: the key features listed for BECTS epilepsy are a copy of those listed for absence epilepsy. I was also surprised to see a large table on the differential diagnosis on megalencephaly in the chapter devoted to hydrocephaly, which was covered very briefly. Further discrepancies from UK paediatric practice includes the suggestion of neuroimaging after a first seizure and EEG "if you suspect epilepsy".

Despite these minor negative points the book is written in a clear and concise way and is easy to read. It will appeal to a wide readership, particularly to paediatricians in training, medical students, specialist nurses, general practitioners, adult neurologists and anyone who wants to develop their interest in paediatric neurology. The book certainly achieves its aim as it gives the reader an introduction to different cases in paediatric neurology, a very challenging and complex discipline. It will definitely find its place on my bookshelf. I would prefer, however, to carry the 'Oxford Specialist Handbook in Paediatric Neurology' around with me on the wards. ♦



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Author: GL Holmes. Published by: Oxford University Press (2011). ISBN: 9780195394580. Price: £17.00.

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associated with the disorder; genetic aspects of epilepsy; and the management in resource-poor settings. Professor [name] holds the UCL Established Chair of Epilepsy, and by the National Society For Epilepsy.

"There is no one more deserving of this honour. Trudie has worked hard for children with the symptoms of sudden loss of consciousness. I am very impressed by the energy and passion she brings to her work in the field of heart rhythm disturbances. Her work has improved the quality

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Medical Rehabilitation in 2011 and Beyond

Review of the report produced by the Royal College of Physicians and the British Society of Rehabilitation Medicine



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Medical rehabilitation (RM) in 2011 and beyond is the fourth report jointly introduced by the Royal College of Physicians (RCP) and the British Society of Rehabilitation Medicine (BSRM). It aims to clarify the role of RM, providing an up to date description of the specialty for the commissioners, providers, planners and service users. This report also highlights the potential development of high-quality service within the principles of the National Service Framework (NSF) for long-term conditions specifying the cost effectiveness of RM. In this context, long-term conditions can be of sudden onset where catastrophic onset is followed by variable degrees of recovery (e.g. brain or spinal cord injuries), intermittent with unpredictability (e.g. relapsing remitting multiple sclerosis), progressive (e.g. progressive multiple sclerosis and motor neuron diseases) or stable but usually with variable needs throughout life due to the superimposed effects of ageing (e.g. cerebral palsy)

The NSF produced a set of quality requirements in 2005 to be achieved over a 10-year period.¹ It provides a life-long user-centred approach for all RM services. Originally the NSF focuses on neurological long-term condition but is it widely applicable? Figure 1 illustrates how the NSF's 11 quality requirements (QR) fit along the care pathway, capturing the flow from early access to RM into an integrated community-based care provision.

Historically, funding for RM services has undergone a series of changes, from centralised budget controlled by health authorities and then were displaced by primary care trusts (PCTs) followed

by payment by results (PbR), practice-based commissioning and world-class commissioning. The impact of the rapidly changing NHS with the introduction of GP commissioning and the provision of foundation status to all providers is far from clear on RM service provision.² The authors of this report acknowledge the need for updating it after the full implementation of GP commissioning in April 2013.

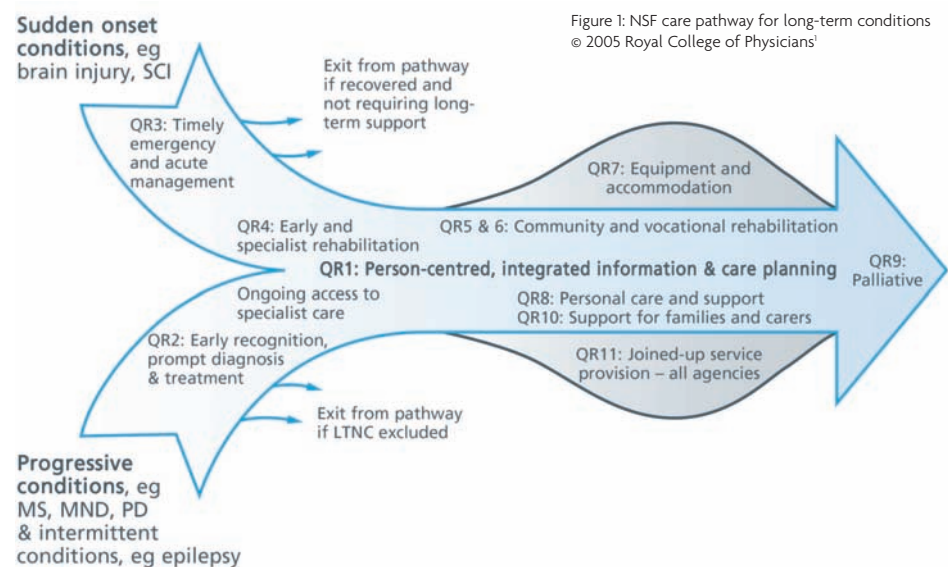
The report explores the following seven domains;

I. Patients and carer perspectives

The majority of people receiving specialist rehabilitation services have highly complex, multi-system needs with huge implications on the patients and their families and care givers. There is a need for a variable complicated adjustment process, especially when the condition is of a sudden onset or when the patient involved is young. Personalised care is therefore the ethos of RM. The specialty manages complex conditions and the rehabilitation interventions are expensive but contribute to supporting and enabling the patients to the fullest and create new meaning in their lives.

II. The principles of RM

RM is a challenging specialty that requires detailed knowledge of the management of various body systems and therefore is not an organ specific specialty. Training in RM includes exposure to psychology, education, law and ethics in addition to acquiring specialist skills in



spasticity and posture management, gait analysis and enabling technology. The clinical practice of RM broadly divides into neurological rehabilitation (including spinal cord injuries) and musculoskeletal rehabilitation (including complex amputee rehabilitation and prosthetics).

The World Health Organisation's International Classification of Functioning (ICF) highlights the dimensions of RM practice and focuses the rehabilitation input on dealing with the person's impairment, level of activity and participation in the society.³ This model of practice accounts for the personal, cultural and environmental issues as well as the impact of the disease (impairment) on the person's life (Figure 2).

The report highlights the role of RM in vocational services. Historically, the role played by health professionals in the UK in supporting patients' employment has been neglected.⁴ However, with the publication of the "Healthcare Professionals Consensus Statement" in 2008, the UK situation began to change.⁵ RM specialists play an important role in supporting their service user's employment on the following domains;

- Optimise the potential and health abilities of the disabled employee,
- Provide support and expert reports highlighting those abilities,
- Promote knowledge and access to specialist vocational service to address various work-related benefits and services,
- Facilitate work withdrawal or re-employment when applicable.

III. Clinical pathways of RM practice

The report highlights the integrated role of rehabilitation medicine in neurological and musculoskeletal conditions and acquired limb loss. As an illustrative example; a severe traumatic brain injured patient with complex physical, behavioural and cognitive challenges has been admitted to the intensive care unit in an acute hospital setting. At this stage, RM consultants advise on the management of such issues working alongside the ITU team. Early identification of spasticity and postural management would result in preventing contractures and facilitate further physical rehabilitation. Advising on basic orientations and environmental clues may facilitate the overall care of an agitated patient as well as advising on medications as appropriate.

These patients are then transferred to the neurological rehabilitation unit where the RM consultant takes over the management, where management of ventilation and airways (e.g. tracheostomy weaning) may take place as well as other specialist rehabilitation interventions. This is carried out by the inpatient interdisciplinary team of physiotherapist, occupational therapist, neuropsychologist, and nursing staff.

In some units across the UK the neuropsychologist lead the brain injury rehabilitation unit. These units will accept patients with behavioural and cognitive impairment as the main disability. It is not a common practice in the UK for the mental health teams and psychiatrists to be involved throughout this process.

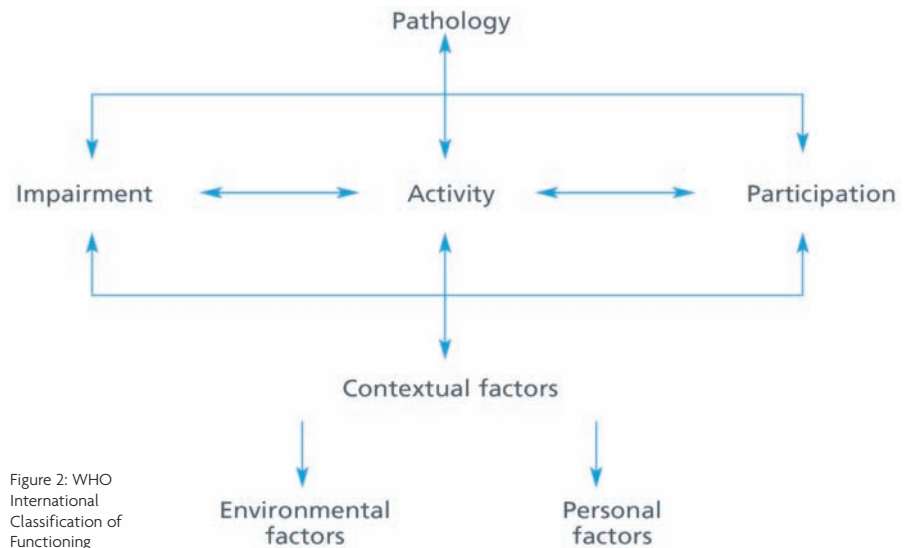


Figure 2: WHO International Classification of Functioning

As these patients progress through the pathway, discharge planning is an important role that can be taken on by the RM team. Integrating these patients back into the community can be a challenging process that requires removal of the boundaries between health, social, educational and vocational services. The majority of these patients would require long term follow up under a RM consultant who could also provide a coordinated approach to the involvement of other specialities if required. Similar pathways were also described in the report in relation to long-term neurological disorders, stroke, spinal cord injuries and amputees.

It is essential with the new health reform and the introduction of GP consortia that commissioners address the complexity of these integrated pathways and the service provision included. Certainly, the non-linear nature of a disabling illness does not fit the traditional 'diagnose-treat-discharge' model of hospital medicine, and therefore will need to be commissioned accordingly.

IV. Summary of the evidence supporting RM

Various robust clinical trials and Cochrane reviews support the effectiveness of rehabilitation medicine. This is despite the challenges in conducting clinical research in the rehabilitation setting. The authors of this report used the GRADE approach to summarise the evidence in acquired brain injury, intermittent neurological conditions and limb loss rehabilitation. For the purpose of this review, I highlight the evidence of effectiveness in rehabilitation following acquired brain injury. This illustrates the approach used to produce the evidence. The key findings from a total of 16 RCTs and 31 non-RCTs were summarised in this report (Figure 3) in addition to referring to RCT based evidence in a Cochrane review.⁶

V. RM standards and outcome monitoring

The BSRM published standards for specialist inpatient and community rehabilitation.^{7,8} These standards were mapped onto the National Service Framework and covered the time for transfer to rehabilitation service from

the acute settings, the minimum staff requirements for specialist rehabilitation service and the key elements of the rehabilitation process, including evaluating the outcomes, audit, research and appraisal within different settings. The key features to identify a specialist rehabilitation service are highlighted in the following:⁹

- The service is led by an accredited RM consultant,
- The service meets the BSRM standards,
- The multidisciplinary team members are accredited and have undergone specialist training in their field of practice to provide these services,
- The team works in an interdisciplinary coordinated way toward an agreed set of goals,
- The service provides a supportive role in the community and local rehabilitation team and have a recognised role in education and training,
- The service collects and reports clinical data to support their practice for all patients including complexity and outcome.

To account for the heterogeneity and the complexity of the service users, the national dataset for specialist rehabilitation was introduced to provide information on the patient characteristics and define the need for specialist service. A hierarchical series of tools has been developed to capture patient complexity (e.g. Rehabilitation Complexity Scale) and various outcomes (e.g. Functional Independent Measure and Goal Attainment Scale) These data form part of the national dataset for specialist rehabilitation which are collated via the UK Rehabilitation Outcome Collaboration (UKROC) database. This can also be used to help in the commissioning of the service and to inform tariff costs for the Department of Health payment by results programme after 2012.

VI. Specific issues for service commissioning

Approximately 10 million people across the UK have a neurological conditions and account for 10% of acute hospital admissions. An estimate of

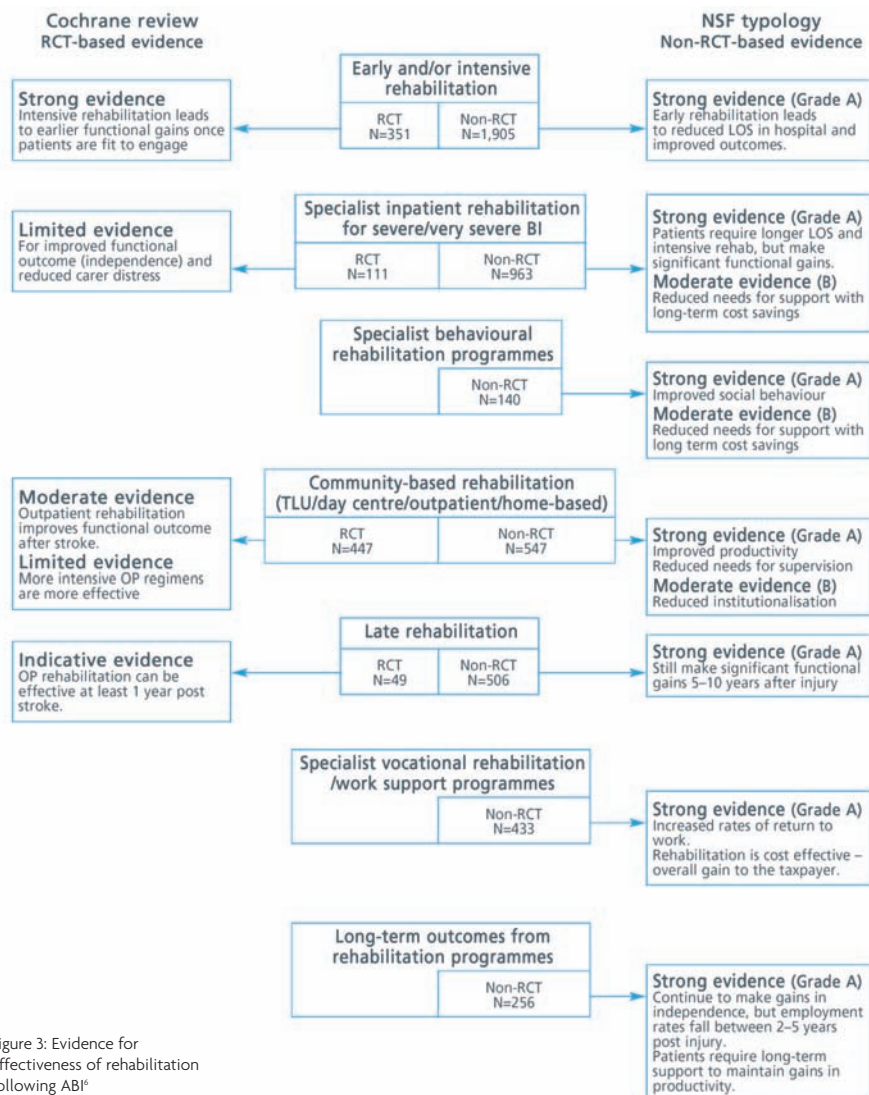


Figure 3: Evidence for effectiveness of rehabilitation following ABI⁶

350,000 of those would require help in their activities of daily living.¹⁰ Changing practice in neurosurgical interventions with more decompressive craniectomies being carried out and the expansion of thrombolytic management for stroke has led to an improvement in the mortality and morbidity rates but also increases the number of complex disabled patients. For example, there is a noticeable increase in neurologically impaired patients requiring long-term tracheostomy who require specialist rehabilitation service for long-term management, possible weaning, planning discharge and community integration. Evidence exists to support the theory that a significant percentage of bed occupancy in acute hospital beds on neurosurgical and neurological wards can be reduced if specialist rehabilitation services have the appropriate capacity.¹¹ Commissioners should not assume that the current provision of RM is sufficient. Addressing those unmet needs could increase the availability of neurological and neurosurgical beds.

The current trends toward stimulating competition in the healthcare market could lead to an increase in the number of provider agencies with their contract being reviewed on a relatively short-term basis. This is likely to undermine the continuity of care which is highly valued by the service users and their care givers.

VII. Future trends and perspectives for the specialty

Current initiatives on acute stroke care, critical illness rehabilitation and trauma care networks highlight the need for specialist rehabilitation intervention. However, they do not describe the downstream situation to cover those people with long-term complex disabilities who require ongoing and recurring need for specialist rehabilitation.

Currently, there are 152 whole time equivalent (WTE) consultants in rehabilitation medicine as well as 25 consultants of different specialities but practise in RM.¹² The BSRM recommends a minimum of 1.5 WTE consultants per 250,000 of the population. A greater number of people are surviving critical conditions and more children with disabilities are surviving to adulthood with ongoing and changing need for specialist rehabilitation services. To account for these changes we require an additional increase of 50% on the current consultant number, with at least 7% in the next two years. Compared to the rest of the European Union, the UK only comes better than Ireland with 0.26 WTE RM consultants per 100,000 population and inferior to the rest of the EU in the provision of RM specialists per capita.¹³

Summary

There is currently little formal specialist input for many people with disabilities living in the community, especially those in institutional care. Pathways for rare long-term neurological disorders are under-developed and can be patchy in different parts of the country (e.g. muscular dystrophy).

On many occasions a RM consultant works in collaboration with other specialists, agencies and service providers on behalf of the patient. The worry with the proposed health reform and GP based commissioning is segmenting the service provision according to named diseases and conditions. We worry that this may have a negative impact on RM service provision. Commissioning may need to consider commissioning according to pathways rather than specific conditions and take into account the need to cross boundaries between providers when dealing with long-term conditions.

The report highlights the need for the commissioners to understand the requirements for disability management and the need for repeated rehabilitation packages to deal with the complex and changing needs faced by those service users with long-term neurological conditions. ♦

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One Size Does Not Fit All: Obtaining informed consent from people with aphasia



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Acknowledgement:

This paper presents independent research commissioned by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-1207-14097). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Obtaining informed consent is difficult when an individual has a communication disability, presenting challenges when involving patients in decisions about their medical treatment, giving power of attorney, participation in research and in discharge planning. There is a growing awareness that people with aphasia can give informed consent if information is provided in an accessible format. However, the range of language disability that can be experienced makes it unlikely that one approach will facilitate understanding of all people with aphasia. In an NIHR Research for Patient Benefit (RfPB) funded project, the authors are piloting a procedure to differentiate methods of making information accessible according to aphasia severity.

Respect for the right of individuals to be fully involved in decisions about their healthcare is laid out in The NHS Constitution (2010).¹ One of the key principles is that "NHS services must reflect the needs and preferences of patients, their families and their carers." In addition it commits to making "decisions in a clear and transparent way, so that patients and the public can understand how services are planned and delivered". These rights are also reflected in The World Medical Association Declaration of Helsinki which sets out the ethical principles that guide medical research.²

Health professionals are aware that a patient must have decision-making capacity as a prerequisite for providing informed consent.³ The Mental Capacity Act (2005) details the abilities that demonstrate capacity to make an informed decision: a) to understand the information relevant to the decision; b) to retain that information; c) to use or weigh that information as part of the process of making the decision; and d) to communicate the decision (whether by talking, using sign language or by any other means).⁴ For people with aphasia, difficulty in communicating a decision verbally or through writing is clear to most professionals who are trying to establish their wishes. More important (but often less obvious) is the fact that the person with aphasia may not have understood the written information or a verbal explanation of the issues to be considered. The Mental Capacity Act states that people should be given the opportunity to make their own decisions as far as possible stating that "A person is not to be regarded as unable to understand the information relevant to a decision if he is able to understand an explanation of it given to him in a way that is appropriate to his circumstances (using simple language, visual aids or any other means)".⁴

The Connect communication disability network has contributed greatly to the inclusion of people with aphasia in decision making by providing

advice on how to produce information that is accessible to people with compromised language skills.⁵ They advocate ideas for making written information easier to understand such as use of short sentences with key words emboldened, pictures to illustrate key ideas and space between each concept.

Such accessible formats are being used by a growing number of health professionals and researchers.^{6,8} However, it is important to emphasise that whilst protecting an individual's right to make autonomous decisions by providing information in a more accessible format using the standard conventions recommended by Connect above, some individuals with aphasia will still not possess the level of language ability required to understand the information in this format. For example, if they are unable to read at all, highlighting key written words will not help inform them. Therefore the authors propose that by acknowledging the existence of a communication disorder and applying a standard set of conventions for making information accessible, we cannot assume that we have adequately informed the specific individual we are interacting with. In order to provide information in a way that is consistent with the individual's level of language, it is necessary to be familiar with the profile and severity of their abilities. Although a full assessment of language is a complex process and requires skilled speech and language therapists, communication screening tests for other health professionals have been validated, for example the Frenchay Aphasia Screening Test⁹ and the Sheffield Screening Test for Acquired Language Disorders.¹⁰ These screening tests indicate the presence and severity of aphasia and so give an indication of the person's communication ability. The procedure being piloted in the RfPB funded project tailors the information giving process to the needs of the individual as follows:

The amount of spoken and written information the individual understands is established through a screening test. Expressive difficulties are determined along with strategies that help the individual to express themselves effectively. Provision of information is then matched to the level of language ability in the following way:

1. If written paragraphs are fully understood a written information sheet is provided using lay terminology with key ideas highlighted. (If written paragraphs are understood but it is time consuming or effortful for the individual, they are given the option of reading information using the standard aphasia friendly conventions)
2. Where the individual understands at least three

key words in a written sentence, e.g. 'Point to the floor, the ceiling and the window'. Information is provided using the full range of standard aphasia friendly conventions advocated by Connect: removing jargon and acronyms and using straight forward language; keeping one main idea per sentence; using active not passive sentences; using bullet points rather than blocks of text; using a question and answer format; using a plain, clear font in size 14 pt; use of plenty of white space; use of relevant and respectful pictures or diagrams to help get the message across and providing summaries of key points.

- Where the aphasia limits the individual to understanding only two key written or spoken words in a sentence, e.g. 'touch your head and your knee', the standard aphasia friendly format may be difficult to interpret without additional support. For these individuals a 'total communication approach' is used whereby each key idea is presented on a separate powerpoint slide using key written words and illustrations or animations. The visual presentation of the information is also supported by spoken explanations, drawing and gesture.
- Where aphasia is more severe and less than two key written or spoken words are understood, the authors suggest that it will be difficult to be sure that we have fully informed the individual of important concepts such as their right to withdraw without affecting future treatment, or concepts that are outside of the immediate environment such as implications of discharge choices. In this case simple pictures and key words, or a short video clip are used to inform the individual about the key topic area and to establish their general feelings about it. Fully informed consent is then sought from a

relative or carer who is given the complete information.

These different methods of providing information were approved by the Bradford ethics committee in advance of piloting them in the RFPB funded study.

Part of the consent process involves the individual asking questions to ensure full understanding of what is going to happen. When the ability to speak is compromised asking questions is difficult. The procedure being piloted encourages the individual to describe a situation if they can't find the right words, or to use gesture, point to pictures or draw. If their speech is difficult to understand, asking them to slow down or write key words can help. Stein et al recommend a process of facilitated consent whereby a person who knows the individual's history, values and preferences asks questions that the individual would ask if he/she could do this easily.³

Decision making capacity as defined by the Mental Capacity Act is specific to a particular decision being made at a specific time. Once information has been presented in a format that is most consistent with the individual's ability to understand written and spoken language, strategies can be used to ensure that the specific information has been understood before taking consent. These include presenting forced alternatives, e.g. 'Are we going to give you a tablet or a questionnaire?', 'If you want to stop, do you have to carry on, yes or no?'. For participants who have reduced understanding of spoken language, pictures can be provided to sort according to their relevance to the information given. Additionally, pictures can be given for the participant to sequence the order in which events will happen.

Where individuals with severe aphasia do not demonstrate understanding of the decisions to be made, or of their implications, the Mental Capacity Act states that a decision should be made in the individual's best

interest and that the decision should be the least restrictive of their basic rights and freedoms.⁴ People involved in caring for the individual who lacks capacity should be consulted and where there are no family members or close friends, an independent mental capacity advocate (IMCA) can be appointed to speak on the patient's behalf.

In summary, this article proposes ways of presenting information consistent with different severities of aphasia, strategies for checking information has been understood and ways to identify those who are unlikely to be able to provide informed consent. ♦

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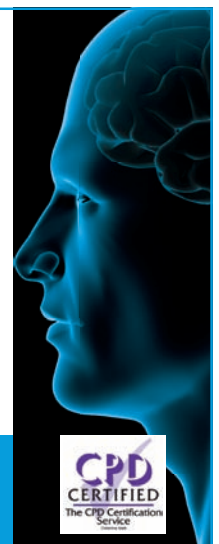
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www.cbituk.org

Ninth European Paediatric Neurology Society
11-14 May, 2011; Cavtat (Dubrovnik), Croatia
E. epns2011@gmail.com
www.epns2011.com

STARS Cardiac Update Course
12 May, 2011; Leicester, UK
www.stars.org.uk/news-events/events

Irish Neurological Association Meeting 2011
12-13 May, 2011; Sligo, Ireland
E. admin@iicn.ie

EFNS Academy 2011
12-15 May, 2011; Stare Splyvy, Czech Republic
E. pragueoffice@efns.org
www.efns.org

25th Annual PSG Symposium on Etiology, Pathogenesis, and Treatment of Parkinson's Disease and Other Movement
13 May, 2011; Irving, USA
www.parkinson-study-group.org

Education

17 May, 2011; Birmingham, UK
E. louisewilkinson@cbituk.org
www.cbituk.org

EFNS Regional Teaching Course – Yekatarinburg
May 18–20, 2011; Yekatarinburg, Russia
www.efns.org

Transient Loss of Consciousness (TLoC) and Epilepsy
18 May, 2011; London, UK
http://events.rcplondon.ac.uk/

SCE Examination for Neurology
18 May, 2011; London, UK
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STARS Cardiac Update Course
20 May, 2011; Oxford, UK
www.stars.org.uk/news-events/events

Executive Function

20 May 2011; Cambridge, UK
T. 01353 652173
E. Rachel.everett@ozc.nhs.uk

6th Invest in ME International ME/CFS Conference 2011

20 May, 2011; London, UK
www.investinme.org

BITs 2nd Annual World Conference of NeuroTalk 2011

22-25 May, 2011; Dalian, China
Rose@bit-neurotalk.com
www.bitlifesciences.com/neurotalk2011/

XX European Stroke Conference

24-27 May, 2011; Hamburg Germany
www.eurostroke.eu

25th International Symposium on Cerebral Blood Flow, Metabolism and Function & 10th International Conference on Qualification of Brain Function with PET

25-28 May, 2011; Barcelona, Spain
www.kenes.com/brain

International Conference on Cognitive and Neural Systems Engineering
25-27 May, 2011; Tokyo, Japan
E. alerts@waset.org
www.waset.org/conferences/2011/tokyo/iccns/

A 21st century review of complex Parkinson's therapy
27 May, 2011; Cambridge, UK
E. register@apo-go.co.uk

Magstim/University of Oxford TMS Summer School
28-29 May, 2011; Oxford, UK
E. tmsschool@fmrib.ox.ac.uk

Cognitive Rehabilitation Workshop
28-29 May, 2011; Madrid, Spain
E. isabelvq@hotmail.com
www.brainretraining.co.uk

21st Meeting of the European Neurological Society (ENS 2011)
28-31 May, 2011; Lisbon, Portugal
E. info@ensinfo.org
http://www.ensinfo.org/

June

One day symposium: Parkinson's disease and other movement disorders
1 June, 2011; London, UK
www.rsm.ac.uk

Neurogenesis 2011

2 June, 2011; Matsushima machi, Japan
events@abcam.com

7th Joint Annual Meeting of Austrian, German and Swiss League against Epilepsy
1-4 June, 2011; Graz, Austria
E. epilepsie2011@comeinnsbruck.at
www.epilepsie-graz2011.at

15th International Congress Parkinson's Disease and Movement Disorders
5-9 June, 2011; Toronto, Canada
E. info.congressi@pandani.it
http://www.pandaniviaggi.it/

FENS-IBRO Summer School, Development and plasticity of cortical representation
5-10 June, 2011; Bertinoro, Italy
E. tanja.butzek@fens.org
http://fens.mdc-berlin.de/fens-ibro-schools/2010/schools/read.php?id=2055

8th Annual World Congress on Brain, Spinal Cord Mapping & Image Guided Therapy
8-10 June, 2011; San Francisco, USA
www.worldbrainmapping.org/abstract

Understanding Brain Injury

10 June 2011; Cambridge, UK
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E. Rachel.everett@ozc.nhs.uk

Cognitive Rehabilitation Workshop

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E. enquiries@brainretraining.co.uk
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European Pain School 2011: Bridging molecules and mind

12-19 June, 2011; Siena, Italy
E. tanja.butzek@fens.org
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EFNS Regional Teaching Course – Lviv
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E. jillie.abbott@btinternet.com
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E. petra.novotny@wolfstiftung.org
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E. tanja.butzek@fens.org
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Metabolic aspects of chronic brain diseases
20-26 June, 2011; Reimsburg, Germany
E. tanja.butzek@fens.org
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ASES - Adriatic Summer Epilepsy School, International Epilepsy Teaching Course
22-26 June, 2011; Dubrovnik, Croatia
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15th Congress of the International Headache Society
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Insight Workshop
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E. lipingsister@gmail.com

July

BSRM/SRR Joint Summer Meeting
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E. admin@brsm.co.uk

Techniques & Applications of Molecular Biology
4-7 July, 2011; Warwick, UK
E. Charlotte.Mooney@warwick.ac.uk

11th ESNi Course - European School of Neuroimmunology
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www.warwick.ac.uk/go/lifescienceshortcourses

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E. keinstein@mednet.ucla.edu
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IBRO 2011
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SiNAPSA Neuroscience Conference
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E. tanja.butzek@fens.org
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Cognitive Rehabilitation
15 July 2011; Cambridge, UKT. 01353 652173
E. Rachel.everett@ozc.nhs.uk

Human Brain Anatomy Course
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August

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September

European synapse summer school
4-23 September, 2011; Bordeaux, France
E. tanja.butzek@fens.org
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10-13 September, 2011; Budapest, Hungary
E. headoffice@efns.org
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Professor José M Ferro.

Dear Colleagues and ENS Members

It is an honour and a privilege to invite you to the 21st Meeting of the European Neurological Society in Lisbon. It is the first time that the ENS meets in Portugal. Lisbon was a natural choice not only because of the facilities available for international meetings, but also because of its charm, its unique light, its multicultural ambience and its splendid geographical location, surrounded by the River Tagus, the Atlantic Ocean and the Cascais-Sintra Natural Park.

The ENS Meeting offers an exclusive opportunity for excellent continuous education in all fields of neurology, both for practising neurologists and for young neurologists in training.

The ENS meeting is also an international stage where those devoted to clinical or translational research can present and discuss the results of their work in an open, friendly but testing environment.

Lisbon and its surroundings offer the participants of the 21st ENS Meeting a vast display of activities to enjoy in the pre- and post-meeting hours or days. Whether walking in the narrow streets of Alfama, relaxing on an esplanade by the river, dining out on delicious traditional fare or on Portuguese new-style cuisine, or exploring the vibrant night-life of Lisbon, participants will enjoy the city's warmth and atmosphere and imbibe its history and culture.

We thank the Administrative ENS Office at Congrex Switzerland for making all necessary preparations for this meeting, to ensure this is a special and memorable event for all participants.

On behalf of the Organizing Committee of the 21st ENS Meeting, it is a pleasure to welcome you to Lisbon in May 2011.

*Professor José M Ferro
Chairperson of the 21st ENS Meeting*

The Scientific Programme of the ENS 2011 annual meeting is designed to offer a whole perspective on what is state-of-the art in the field of neurology. This year the Scientific Programme includes seven symposia:

Joint Symposium of the ENS and the Portuguese Neurological Society:

Saturday, 28 May 2011 (17.15-18.45)

Familial amyloid polyneuropathy

Chairs: G. Said (Paris, FR), V. Oliveira (Lisbon, PT)

Clinical aspects and management – I. Conceicao (Lisbon, PT)

The genetics of FAP: A global problem – V. Planté-Bordeneuve (Paris, FR)

Treatment of FAP by liver transplantation – O. Suhr (Umea, SE)

New pharmacological treatment – T. Coelho (Porto, PT)

Presidential Symposium:

Sunday, 29 May 2011 (17.30-19.30)

Treatment of muscle diseases: The future is already here

Chair: Z. Argov (Jerusalem, IL)

Can we bypass a muscle metabolic defect? – Z. Argov (Jerusalem, IL)

Exercise therapy in muscle disease: A current overview

– T. Taivassalo (Montreal, CA)

Antisense therapy of muscular dystrophies – F. Muntoni (London, UK)

Gene therapy for myopathies – J. Mendell (Columbus, US)

Symposium: Monday, 30 May 2011 (09.00-11.00)

Molecular and cellular mechanisms of ischaemic stroke

Chair: G. Stoll (Würzburg, DE), J. Ferro (Lisbon, PT)

Novel molecular targets for acute stroke treatment – G. Stoll (Würzburg, DE)

Brain-immune interactions, infection, and inflammation in acute stroke

– X. Urra (Barcelona, ES)

Hypothermia: From animal models and translation to humans

– S. Schwab (Erlangen, DE)

Stem cells in experimental stroke: Translation to humans?

– E. Díez Tejedor (Madrid, ES)

Symposium: Monday, 30 May 2011 (09.00-11.00)

Psychiatric aspects of neurological disorders

Chair: H. Förstl (Munich, DE)

Behaviour and theory of mind in frontotemporal dementia

– H. Förstl (Munich, DE)

Psychiatric aspects of PSP, MSA and ALS – A.C. Ludolph (UlM, DE)

Psychiatric symptoms in Parkinson's disease – E. Zuckica (Prague, CZ)

Behavioural and psychological symptoms of dementia (BPSD) in

Alzheimer's disease: Update on management – R. Heun (Birmingham, UK)

Symposium: Tuesday, 31 May 2011 (09.00 – 11.00)

Metals and movement disorders

Chair: P. Taba (Tartu, EE)

Wilson's disease – W.H. Oertel (Marburg, DE)

Neurodegeneration with brain iron accumulation (NBIA) syndroms

– K. Bhatia (London, UK)

Manganese-related movement disorders – P. Taba (Tartu, EE)

Metal ions and neuro-degeneration – P. Jenner (London, UK)

Symposium:

Tuesday, 31 May 2011 (09.00 – 11.00)

Biomarkers for diagnosis, prognosis and response to treatment in MS

Chair: R. Martin (Hamburg, DE)

Transcriptomics – R. Martin (Hamburg, DE)

Genetic markers – J. Hillert (Stockholm, SE)

CSF markers – G. Giovannoni (London, UK)

Magnetic resonance imaging – M. Filippi (Milan, IT)

Symposium:

Tuesday, 31 May 2011 (17.30 – 19.30)

G rard Said Farewell Symposium

Welcome – G. Moonen

Electrophysiological studies in peripheral nerve disorders

– C. Krarup (Copenhagen, DK)

Diabetic neuropathy – G. Llewelyn

Of MAG and neuropathy – A. Steck (Basel, CH)

Is nerve biopsy still useful? – G. Said (Paris, FR)

Closing remarks – Z. Argov (Jerusalem, IL)

In addition to the symposia, the scientific programme includes four poster sessions and various oral sessions of free communications. The ENS has always been known for the practical and educational side of its annual meetings. This year again, the participants have the chance to hear about the latest techniques and tools in practice in teaching courses, workshops, interactive case presentations and practical sessions.

Teaching Courses

The teaching courses are led by leading European experts who share their personal experiences and guide the participants through all aspects of neurology. To name just a few highlights: “*Key differential diagnosis and management issues*” will focus on the clinically isolated syndrome which in many cases are diagnosed as early MS, stroke in the young, and the ALS-suggestive motor neuron symptoms. Especially the question who should be treated how and when, will be addressed. The “*Non-Alzheimer diseases*” course will provide an update on the diagnosis, criteria, pathophysiology and treatments of the main non-Alzheimer dementias, examining the metabolic and vascular causes of dementia, frontotemporal lobar degeneration, and dementia with Lewy bodies. Prognosis and management differ, and the differential diagnosis is necessary to assess disease-modifying therapeutic strategies. The teaching course “*Effects and complications of long-term treatment in MS*” will address the development of more treatment options which raises questions concerning their long term-effects. The course will conclude with a discussion on prospective long-term follow up studies and risk management plans. The goal of the course “*Advances in the diagnosis of seizures and epilepsy*” will be to update the audience on semiological aspects of seizures, to give information on the added value of EEG and current optimum MRI protocols and to demonstrate the current state-of-the art of MEG in epilepsy. Three teaching courses will be given in a collaboration between the ENS and AAN: “*Update in neuro-oncology*”, “*White matters: Inflammatory and genetic/metabolic leukoencephalopathies in young patients*” and “*The neurology of unconsciousness*”.

Workshops

The ENS Subcommittees have organised various workshops covering all fields of neurology. The programme blends clinical neurology, diagnostic approaches and treatment on a variety of neurological aspects. The faculty – all noted experts in their fields – will cover individual topics over a 90 – minute period.

Subjective memory complaints are an extremely frequent cause of neurological consultation, and represent the typical presentation of several neurodegenerative disorders, Alzheimer's disease in the first place. The present evidence on differential diagnoses among the causes of subjective memory complaints, neurological and psychiatric, will be reviewed in the workshop “*How to manage subjective memory complaints*”. The workshop “*fMRI to probe motor recovery from stroke rehabilitation*” will critically discuss the role of fMRI to probe motor recovery after stroke, provide information concerning the pathophysiologic underpinnings, technical possibilities and challenges and summarises the converging evidence from the studies available so far. Within the workshop “*Assessment of regional atrophy in clinical neurology*” useful technical and practical hints on the methods of analysis of regional atrophy will be given for clinicians and researchers. Suggestions on how to apply MRI-based methods and post-processing analysis tools in clinical neurology will be given. The workshop “*Pimp up your residency*” aims to discuss current challenges that neurology residents and medical students face, with a view to help their training, to give hands-on information for a training period abroad and tips for the major European fellowships. During this workshop an update on the European neurology e-learning project will also be presented.

Interactive Case Presentations


Participants are invited to present and discuss personal cases with their colleagues. Through an interactive voting system, different opinions can be collected. The following topics will be covered: Clinical pitfalls, disorder of gait, disorders of high cortical functions, neuroradiological pitfalls, paroxysmal disorders awake, and paroxysmal disorders from sleep.

Practical Sessions in Clinical Neurophysiology

Practical demonstrations in the field of clinical neurophysiology will take place in order to practice diagnostic skills. These sessions will encourage attendees to raise topics for discussion and debate on EMG, nerve conduction studies, reflex studies and SFEMG.

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- Questions & answers and summary
X. Montalban

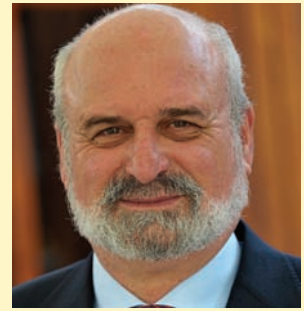
The Presidential Symposium: Treatment of Muscle Diseases: the future is already here

The aim of this symposium is to present the major developments in therapy of human hereditary myopathies.

Introduction

The field of myology has for a long time been short of therapeutic interventions. Apart from the inflammatory (autoimmune) conditions, most of the management of the hereditary myopathies was related to orthopedic complications and general physical therapy. In recent years therapy in myopathies has been a rapidly evolving field that has reached human trials.

Progress is based on accumulated knowledge from animal models and those methods that matured to be applied to patients are currently being tested. In this year's ENS Presidential Symposium, the scientific basis and the current status of metabolic therapies, exercise prescriptions, antisense oligonucleotide use and viral-mediated gene therapy will be discussed.



**Professor Zohar Argov,
ENS President 2011-2,**

is a Professor of Neurology, and Kanrich Chair of Neuromuscular Diseases at the Hadassah-Hebrew University Medical Center, Jerusalem, Israel. Also he is an Adjunct Professor of Neurology at the Montreal Neurological Institute and Chair of the Israeli Society of Neuromuscular Diseases.

Can we bypass a muscle metabolic defect? (Zohar Argov, Jerusalem, Israel)

The metabolic myopathies seem to be more amenable to treatment once the biochemical defect is identified. Some of the conditions cause mainly exercise intolerance and its improvement can be regarded as therapeutic success. In others, muscle weakness and degeneration occurs and functional and strength improvement is the goal.

Therapy of such disorders can be achieved through enzyme replacement (e.g. Pompe's

disease) or its upregulation (e.g. bezafibrate in CPT2 deficiency). Other methods include: 1. supplementation of a missing compound (e.g. CoQ10 which is effective only in primary Q10 deficiency but is given to most patients with other mitochondrial disorders); 2. use of metabolic 'cocktails' to increase the muscle oxidative capacity of muscle (combinations of oxygen species scavengers like menadione with K3, vitamin C, riboflavin, carnitine and creatine); 3. increasing availability of compen-

satory fuel sources (e.g. sucrose given before exercise or a carbohydrate-rich diet in McArdle's disease). 4. providing metabolic intermediates that are downstream to the enzymatic defective site (e.g. ManNac or sialic acid for HIBM with defects in GNE, an enzyme in the synthetic pathway of sialic acid).

Because of the rarity of metabolic myopathies, no proper double blind studies were performed to assess these therapies and recommend an agreed protocol.

Exercise therapy in muscle disease: a current overview (Tanja Taivassalo, Montreal, Canada)

Exercise intolerance is a common clinical presentation in neuromuscular disorders, resulting from the primary disease process or a secondary effect of either cardiovascular deconditioning or muscle disuse due to adoption of sedentary lifestyle. Exercise training is well-established to counter the effects of deconditioning in healthy people and various chronic disease conditions. It has traditionally been discouraged for patients with muscle disorders for fear of exacerbating symptoms as well as lack of evidence-based knowledge on the effects of strength or aerobic exercise on the given disease process. Progress has recently been made regarding the safety and efficacy of exercise training as therapy in various muscle diseases (metabolic and inflammatory myopathies and muscular dystrophies). These studies have assessed the ability of the exercise stimulus (aerobic training, AT, at 60-80% peak heart rate, 20-40 minutes 3 times per week or strength training, ST, at variable intensities 2 to 3 times per week) to reverse deconditioning and affect the disease process.

In GSD type V (McArdle's disease), moderate intensity AT improved exercise capacity (by increasing circulatory delivery

and mitochondrial metabolism of blood-borne fuels) without side effects. Despite these training adaptations, fuel availability continued to limit oxygen utilization and exercise capacity. Due to the concern for muscle injury in this population, the effects of ST on muscle strength were not evaluated.

In a handful of studies assessing exercise therapy in mitochondrial myopathies, AT and ST reversed deconditioning and increased peak exercise capacity as well as muscle strength. The specific effects of AT on the disease process (levels of mutant mitochondrial DNA in heteroplasmic defects or enzymatic deficiency in nuclearencoded defects) are still unresolved. An alternate rationale for ST in certain heteroplasmic mutations involves the activation of satellite cells in response to muscle overload or injury, and is currently being assessed as a strategy to increase levels of wild-type mitochondrial DNA.

Patients with sporadic inclusion body myositis improved aerobic capacity and muscle strength as a result of combined AT and low-intensity ST of the upper and lower limbs without unfavorable muscle symptoms or further increases in baseline CK. However, signif-

icant increases in muscle size were not detected. To achieve greater gains in muscle size and therefore strength, a novel strategy using moderate-intensity ST with vascular occlusion increased muscle cross-sectional area and strength in a single patient with sporadic IBM.

Limited studies assessing exercise training in muscular dystrophies showed that low-intensity AT improved peak exercise capacity with no signs of muscle damage in facioscapulohumeral dystrophy (FSHD), Becker's and myotonic dystrophy. In both FSHD and myotonic dystrophy, moderate-intensity ST is reported to have no negative effects, however improvements in muscle strength or size are limited or non-existent. The application of neuromuscular electrical stimulation, as a surrogate for ST in patients with severe muscle weakness, has recently been reported to be well-tolerated and resulted in improved muscle strength in FSHD.

In conclusion, despite the initial progress made thus far, there is an urgent need for larger, randomised controlled studies to confirm the safety and develop specific exercise guidelines to optimise efficacy of exercise therapy in various muscle diseases.

Antisense oligonucleotide therapy for muscular dystrophies (Francesco Muntoni, London, UK)

The improved understanding of the genetic basis and molecular events leading to muscle degeneration in muscular dystrophies, coupled with advances in antisense oligomers, has moved very rapidly in the last decade from in vitro experiments and in-vivo studies in appropriate animal models to phase I; IIa; IIb and now III clinical trials in Duchenne muscular dystrophy (DMD), the most common of the severe and childhood onset muscular dystrophies. The pace of the development of these novel genetic approaches to treat muscular dystrophies is exciting and one of the fastest in recent drug development programmes.

The research program that has paved the way to the therapeutic developments for various muscular dystrophies is the one in DMD: the first description of the use of antisense oligonucleotides to modify the splicing of the dystrophin gene in cultured mdx muscle cells was only published in 1998. Less than 10 years later in 2007,

the results of the first intramuscular 'proof of concept' study in DMD boys was published, followed by a second one in 2009. During the course of 2009-2010 two separate repeated systemic dosing studies using 2 different antisense oligomers have been completed. Two large international randomised placebo-controlled studies were recently initiated. The outcome of these studies is expected by early 2012; and additional studies are being planned.

Preclinical studies in myotonic dystrophy are also rapidly advancing, followed by also attempts to utilise antisense oligomers in other, less common muscular dystrophy variants, for example in LGMD2B. In parallel to the pioneering human studies using these 'first generation' chemistries, experimental work focused on optimising the efficacy of new generation antisense is very rapidly progressing, with unparalleled efficacy in preclinical models.

The status of the art of the clinical and preclinical work being performed in this field will be updated.

Gene Therapy: Myth, Milestones, and Momentum (Jerry R. Mendell, (Columbus, Ohio, USA)

Therapeutic options for muscular dystrophy are limited. Presently only corticosteroids have been found to benefit boys with Duchenne muscular dystrophy (DMD), although the results are modest and side effects significant. The translational research community has introduced molecular strategies to potentially enhance mutant gene expression through exon skipping, mutation suppression, and gene replacement. Each of these approaches has merit and is being tested in clinical trials. For gene replacement therapy, adeno-associated virus (AAV) has been established as a safe vehicle for gene transfer with the recognition that pre-existing exposure to this virus can present obstacles. As the most common severe form of inherited muscle disease, DMD has been a particular target for gene therapists. In the first AAV-mediated gene therapy trial for this disease, a surprising finding was that hidden epitopes of expressed dystrophin, usually found on revertant fibers, proved to be immunogenic for some individuals. It had previously been considered that dystrophin expressed on revertant fibers was tolerizing. The lesson learned

is that patients can be screened prior to participation, paving the way for safe gene transfer. Clinical experience has also demonstrated that transfer of mini-dystrophin genes must be carefully matched with endogenous DMD gene deletions to avoid expression of novel immunogenic epitopes.

A major milestone for gene therapy was the first successful gene transfer using AAV to deliver the alpha-sarcoglycan gene in one form of limb girdle dystrophy- LGMD2D. Sustained gene expression for six months was achieved following intramuscular gene transfer. Further advantages accrued through the use of a muscle specific promoter. An exception was a patient exhibiting pre-existing AAV neutralising antibody that it will be necessary to avoid in future trials. Other strategies for gene transfer are poised for clinical trials, including building muscle size and strength through AAV-mediated gene transfer of follistatin. In addition, AAV5 is uniquely capable of transferring genes that exceed the usual packaging limit of ~5kb, an important obstacle to overcome for therapy of disorders due to big gene mutation.

Pharmaceutical Industry Satellite Symposia Schedules at the ENS Meeting

Advances in novel drug development and treatments by the pharmaceutical industry for a wide spectrum of neurological disorders has taken on a fast pace and there is an increasing need for comprehensive satellite symposia. Participants will be informed as to advances currently taking place in the pharmaceutical industry, along with insights as to the possibilities of future innovations. Topics and schedules of these satellite symposia are given below (as per 11 February 2011).

Sunday, 29 May 2011

Merck Serono – 12:00-13:30

It's a marathon, not a sprint. Clinical decision-making to support patients throughout the MS journey

Chair: M. Sandberg-Wolheim, Lund / SE; M.J. Sá, Porto / PT

UCB – 12:00-13:00

Sleep and CNS diseases

Chair: C. Bassetti, Zurich and Lugano / CH

Monday, 30 May 2011

Novartis – 11:45 13:15

Fingolimod: MS treatment transformation

Chair: J. Hillert, Stockholm / SE; J. Correia de Sá, Lisbon / PT

SSIF – 11:45 13:15

Advances in frontotemporal dementias

Chair: G. Comi, Milan / IT; S. Cappa, Milan / IT

UCB – 11:45 13:15

Restore what Parkinson's disease takes away

Chair: K. Ray-Chaudhuri, London / UK

Biogen Idec – 17:15-18:45

Addressing patient needs today and tomorrow (MS)

Chair: J. de Sá, Lisbon / PT (TBC)

Tuesday, 31 May 2011

Teva – 11:45-13:15

Laquinimod: A step closer to a novel oral treatment option for patients with MS

Chair: L. Sousa, Coimbra / PT

The ENS meeting offers the opportunity to present research results to a large number of colleagues from the entire spectrum of neurology. Specialist areas often have numerous links to various fields of inquiry and the ENS meeting offers the greatest opportunity to encounter colleagues with parallel interests. The following 3 abstracts have received the best grades. These abstracts and all other accepted abstracts for the 21st ENS meeting are published in the supplement of the *Journal of Neurology*.

Disorders of consciousness

PROgnosis of PostAnoxic Coma after treatment with hypothermia: results of PROPACII, a multi-centre prospective cohort study

A. Bouwes, J.M. Binnekade, M.A. Kuiper, F.H. Bosch, D.F. Zandstra, A.C. Toornvliet, H.S. Moeniralam, B.M. Kors, J.H. Koelman, M.M. Verbeek, H.C. Weinstein, A. Hijdra, J. Horn. Academic Medical Center (Amsterdam, NL); Medical Center Leeuwarden (Leeuwarden, NL); Rijnstate Hospital (Arnhem, NL); Onze Lieve Vrouwe Gasthuis (Amsterdam, NL); Medical Center Alkmaar (Alkmaar, NL); St. Antonius Hospital (Nieuwegein, NL); Kennemer Gasthuis (Haarlem, NL); Radboud University Nijmegen Medical Center (Nijmegen, NL); Sint Lucas Andreas Hospital (Amsterdam, NL).

Objectives: Current guidelines for outcome prediction in patients with postanoxic coma after cardiopulmonary resuscitation (CPR) are based on data from patients not treated with hypothermia. New information is required. The Aim of this study was to establish the reliability of neurological examination, neuron-specific enolase (NSE) and median nerve somatosensory evoked potentials (SEP) to predict poor outcome in patients treated with mild hypothermia after CPR.

Methods: Multicentre prospective cohort study, including adult comatose patients, admitted to the ICU after CPR and treated with hypothermia

(32–34°C). Neurological examination (Glasgow Coma Score and brain stem reflexes) was performed 72 hours after CPR. Samples for NSE levels were drawn on admission, 12 hours after reaching target temperature, 36 and 48 hours after CPR. Median nerve SEP was recorded during hypothermia and after rewarming. Neurological outcome was assessed with the Glasgow Outcome Scale (GOS), after 1 week, 1 month and six months. Primary outcome was poor outcome, defined as death, vegetative state or severe disability after six months.

Results: 391 patients were included, 53% had a poor outcome. Absent pupillary light responses

(FPR 1, 95% CI 0-7), corneal reflexes (FPR 1, 95% CI 0-7) and N20 responses in SEP after rewarming (FPR 0, 95% CI 0-18) were reliable predictors. Motor scores 72 hours after CPR and NSE levels were not.

Conclusion: Poor outcome after CPR and therapeutic hypothermia can reliably be predicted by testing brain stem reflexes and SEP. Other methods recommended in current guidelines could possibly lead to inappropriate withdrawal of treatment.

This study was supported by a research grant from The Netherlands Heart Foundation, 2007B039.

Clinical neurophysiology

Assessing cortical effective connectivity in patients with disorders of consciousness

M. Rosanova, O. Gosseries, S. Casarotto, M. Boly, A.G. Casali, MA. Bruno, P. Boveroux, G. Tononi, S. Laureys, M. Massimini. University of Milan (Milan, IT); University of Liege (Liège, BE); University of Wisconsin (Madison, US).

Objectives: Brain-injured patients are considered conscious if they can interact with the environment and unconscious otherwise. As suggested by other works, a key requirement for consciousness is that multiple, specialised cortical areas can interact rapidly and effectively. Here we employ transcranial magnetic stimulation combined with electroencephalography (TMS/EEG) in order to assess cortical effective connectivity at the bedside of brain-injured patients with disorders of consciousness.

Methods: We used a TMS-compatible 60-channels EEG amplifier to record TMS-evoked potentials in 17 brain-injured patients. A first group of 12 patients (Group I) underwent a single TMS/EEG session after one week of behavioral evaluations (Coma Recovery Scale-Revised). Five of these patients were diagnosed as vegetative state (VS),

five were minimally conscious (MCS) and two were in a locked-in syndrome (LIS). A second group of five patients (Group II) were recruited as soon as they awakened from coma and underwent longitudinal TMS/EEG measurements. Three of them recovered consciousness evolving from VS through MCS to emergence from MCS. We stimulated bilaterally the parietal and the frontal lobes in each patient.

Results: In Group I, VS patients, who were open-eyed, behaviorally awake but unresponsive, TMS triggered a stereotypic and local response indicating a breakdown of effective connectivity, similar to the one observed in sleep or anaesthesia. On the contrary, in MCS patients, who showed fluctuating signs of non-reflexive behavior, TMS triggered rapidly changing, widespread responses similar to the ones recorded in LIS and healthy

awake subjects. In Group II, a simple and local response to TMS was also recorded in all patients as soon as they transitioned from coma to VS. In the three patients who recovered consciousness and functional communication, intracortical effective connectivity resurged soon after they switched from VS to MCS as well as they emerged from MCS.

Conclusion: TMS/EEG measurements performed in Group I suggest that clear-cut differences in intracortical effective connectivity underlie the subtle clinical discrimination between VS and MCS patients. TMS/EEG measurements performed in Group II showed that cortical effective connectivity re-emerged in VS patients who recovered consciousness as soon as they recover to MCS. Thus, directly perturbing the brain to assess effective connectivity may represent a sensitive way to uncover a brain's capacity for consciousness.

Child neurology – Poster session

Using functional MRI to assess the effects of a morpheme-based training in dyslexia

D. Gebauer, A. Fink, R. Kargl, G. Reishofer, K. Koschutnig, F. Fazekas, C. Enzinger. Medical University Graz (Graz, AT); Karl-Franzens University Graz (Graz, AT); Dyslexia Institute Graz (Graz, AT).

Objectives: Dyslexia is a neurodevelopmental disorder, associated with a greater risk of school drop-out, unemployment, and emotional and behavioural problems. Approximately 15% of affected children show reading and spelling difficulties. Hence, it is of major importance to

improve the understanding of the underlying brain processes of dyslexia, in order to optimize future interventions. We here set out to assess the effects of a morpheme-based training in dyslexic children on brain function.

Methods: 42 children aged between 9 and 15 years

participated in the study. To assess a specific effect of the training, dyslexic children were divided into a 'Training-Group' (n=14) and a 'Waiting-Group' (n=14). The dyslexic groups were compared to 14 age- and intelligence-matched controls. In pretests, reading and spelling skills, intelligence and person-

ality were assessed. Structural and functional MRI scans were obtained at a 3 Tesla scanner. During fMRI, children had to identify misspelled words, correctly spelled words and pseudowords. The 'Training-Group' received a five-week intensive intervention. After this period, all three groups were again tested behaviorally and re-scanned.

Results: Compared to controls, while processing the presented words, dyslexic children showed significantly increased activation in the right hemisphere and decreased activation of the left fusiform and temporal regions prior to the training. After the intervention, an adjustment of activation pattern to controls was observed in the

'Training-Group', parallel to behavioural improvements.

Conclusion: These results support the concept of training-induced neural plasticity. Initially presumably compensatorily increased right hemispheric activation and decreased left hemispheric activation normalized subsequent to training.

Stroke

Evolution or revolution? 1-year results for mechanical thrombectomy with the Solitaire stent in acute stroke

A. Mpotsaris, M. Bussmeyer, J. Fuehrer, H. Buchner, W. Weber. *Klinikum Vest (Recklinghausen, DE).*

Background: To report the effectiveness of mechanical thrombectomy with the Solitaire stent in severe acute ischaemic stroke in conjunction with intravenous systemic thrombolysis.

Methods: Prospective, ongoing single centre study of patients with acute ischaemic stroke based on proven large artery occlusion via CT-angiography in anterior or posterior circulation. Following strict inclusion criteria patients were triaged for eligibility for mechanical thrombectomy, independently of intravenous thrombolysis with tissue plasminogen activator (rTPA). Clot retrieval was performed with the Solitaire stent (AB and FR, ev3 Inc, Plymouth, MN) with up to 4 maneuvers. NIHSS and mRS scores were assessed on admission, discharge, after 90 days and after

one year. For evaluation of outcome, patients were stratified to early, intermediate and late treatment subgroups.

Results: Up until January 2011 54 patients were eligible for mechanical thrombectomy with the Solitaire stent since October 2009. 92 % had a NIHSS score of ≥ 10 and 96% mRS 4 or 5 on admission. 40 of 54 patients received intravenous rTPA prior to mechanical thrombectomy (bridging technique), 14 were treated with thrombectomy alone. 27 of 54 had tandem stenosis and were a priori stented. Recanalisation rate was 88%; in 50% of cases the first attempt led to recanalization. There were no procedural complications. Overall 37% (20 of 54) patients had a good clinical outcome (mRS ≤ 2) in the 90 days

follow up interval. In the early treatment subgroup (n=21) with recanalization in ≤ 4.5 h from symptom onset good outcome was reached in 50%. Of 13 patients with carotid-T-occlusions 6 had a good outcome after 90 days. Patients who were treated in bridging-technique with intravenous rTPA had a higher NIHSS score reduction (p=0.06) than non-bridging patients. By May 2011 the 1-Year results of 25 patients will be available for analysis.

Conclusions: The combination of rTPA and mechanical thrombectomy is safe. The Solitaire stent can be deployed safely and quickly. The 90 day results are encouraging, especially in combination with i.v. rTPA; the Solitaire may play a key role in further improvement of outcome in severe acute stroke, especially in carotid-T-occlusions.

European Neurological Society: A Leading Force in Europe Neurology: Learning, knowledge, progress and the future

The Society

The European Neurological Society (ENS) was founded in 1986, based on the initiative of Gérard Said, Anita Harding and PK. Thomas. The ENS represents an effort to break away from a national representation to a membership on an individual basis. This emphasis on individuality underlines the importance of expertise in the various fields of neurology, as well as the singular expression of enthusiasm for clinical and experimental neurology. The ENS has now become the most important prominent society for neurologists in Europe and its members excel in the practice and teaching of neurology, including research in which neuroscience plays an important role. The official scientific journal of the ENS is the *Journal of Neurology*, one of the leading publications in this medical discipline.

The role of the ENS

An academic organisation such as the ENS provides the platform from which clinical and experimental neurologists of various subspecialties can interact and exchange their knowledge and expertise. The society aspires to guide neurologists in their decision-making in order to attain the best possible care for patients with neurological disorders.

The aims of the society are

- To provide continuing education in all fields of neurology
- To create a scientific forum for the presentation of original research work for all neurologists
- To guarantee a high level of scientific standard
- To support the younger generation by continuing promotions such as travel grants, fellowship stipends and the Neurologist in Training Offer.

The ENS is especially eager to support, encourage and guide young neurologists. In order to facilitate international contact of young physicians among themselves and with leading experts, participation in our meetings is actively promoted. Every year, travel grants to junior abstract authors whose papers have been accepted for presentation at the meeting are distributed. In addition, the ENS has started the very

successful "Young neurologists in training programme" in 2006, which offers a limited number of grants providing free accommodation (4 nights), free registration and free admission to 3 teaching courses. Accordingly, the ENS annual meeting becomes an attractive forum for young scientists for learning and networking, which enhances the scope of their activities and possibilities.

Furthermore, the ENS has been supporting young neurologists with fellowships for many years. ENS sponsors this programme to provide an opportunity for talented researchers to participate in an exchange of scientific activities between home and host institutions.

Annual meetings

The ENS organises a scientific meeting every year, which provides the ideal platform for continuing education in all fields of neurology, covering a broad spectrum of topics with state-of-the-art lectures by acknowledged experts. The ENS is dedicated to giving the congress attendees the highest quality medical education as well as to open professional education opportunities. The ENS provides a wide range of programme formats, including main symposia, teaching courses, workshops, interactive case presentations and oral and poster sessions.

The ENS 2011 annual meeting will take place in Lisbon, Portugal, 28 – 31 May 2011. This meeting will again be the primary stage for the latest developments in scientific research, where neurologists share and discuss innovative studies.

ENS Subcommittees

The ENS Executive Committee has set up a series of subcommittees in order to increase involvement of ENS members in policy decisions, representative of the diversity within the neurological field. The subcommittees aim to promote and advance the continuing education within their neurological specialties. Each ENS member can join an ENS subcommittee to actively play a part in contributing to the scientific programmes of the ENS annual meetings and to promote the growth and excellence of the subspecialty. The subcommittees serve as a place to exchange ideas and to network, an immensely important point with the increasing globalisation of the world.

Association of British Neurologists Joint Meeting with Neurology Section, Cuban Society of Neurology & Neurosurgery

Conference details: 4-6 April 2011, Havana, Cuba. **Reviewed by:** Heather Angus-Leppan, Ralph Gregory and Martin Rossor, ABN.

One hundred and twenty five delegates from Cuba, 72 from the UK and one each from the USA, Peru and Spain, enjoyed a three day joint conference in Havana, hosted by the respective presidents Professors Enrique de Jongh and Martin Rossor. The delegates included several medical students and a large group of specialist registrars many of whom had received ABN travel bursaries. The conference was held at the Hermanos Ameijeiras Hospital. This is the largest hospital in Cuba with 650 beds. The building was originally built to be the national bank. Following the revolution in 1959 it was unused but with the addition of 12 further floors, was transformed into a hospital in 1982. Delegates were initially welcomed into the vast entrance hall which was originally intended to be a trading floor. The sixty posters were displayed on an elevated area at one end of the hall, while the hospital continued with its busy and well organised activities. Delegates were able to appreciate first hand the excellent health care system that Cubans enjoy. This is free to all citizens, with each primary care physician (family doctor) looking after about 120 families. This has resulted in a perinatal mortality rate, and life expectancy that is comparable with anywhere in the world.

The conference was opened by a lecture from Martin Rossor entitled Clinical Syndromes in Degenerative Dementia. He introduced the concept of "dementia plus", a model we are familiar with when assessing a patient with parkinsonism. The appreciation of what clinical features an individual has, in addition to a memory deficit, enables a reliable clinical diagnosis to be made in many cases. There then followed the first of three sessions where 15 scientific papers from Cuba and the UK were all delivered in impeccable English. Highlights included a paper on presumed nutritional optic and peripheral neuropathy in Cuba and Africa by Gordon Plant. Also known as Strachan's syndrome (pronounced "strawn"), the supposed nutritional deficit remains unclear. It is most likely due to a low protein, normal calorie diet, exacerbated by high energy output. (It occurred at a time when Cubans found themselves with a severe shortage of certain foods and all fuels, so the average Cuban was expending more energy on cycling and walking with less protein available). The last outbreak in Cuba ended in 1993, and similar epidemics have recently been described in Somalia. Ramon Begueria



Professor Enrique de Jongh

presented a paper entitled knowledge attitudes and practice toward epilepsy among adults in Havana which illustrated the same degree of ignorance within the general population that is seen worldwide. Andrew Lees and Eduardo Tolosa delivered a joint lecture on exotic movement disorders which included videos of an East European drug addict with an extrapyramidal syndrome caused by permanganate used in the preparation of ephedrone, and dopa responsive dystonia in a patient with a Park 2 mutation and no clinical evidence of parkinsonism despite a very abnormal DAT scan. The case competition was taken very seriously by the contestants, judges and audience. It was chaired by Colin Mumford in fluent 'Spanglish'. The winner will become the subject of ABN Christmas quizzes as Cinithia

Professor Martin Rossor, ABN President.



Terroba was from Peru! She described a case of internal carotid artery dissection after ergotamine overdose. Kevin Talbot discussed the prospects of a cure for MND and Hadi Manji gave an overview of HIV neurology, which was particularly interesting for our hosts as it is infrequently seen in Cuba. Carlos Santos-Anzorandia gave a presentation on clinical neurophysiology on the island. There are over 50 neurophysiology units, and more than 100 clinical neurophysiologists in Cuba functioning as an integrated network to collect data, using equipment which has been designed and built locally. It transpired that several UK units are using the same equipment exported from Cuba. Jesus Perez-Nellar's paper was entitled 'Tertiary Stroke Unit Managed by Neurologists: the Cuban Experience'. He presented data showing how mortality and length of stay rates had fallen to that of well developed countries since the introduction of multidisciplinary acute stroke units run by neurologists rather than general physicians. This is despite tPA not being available due to cost, reinforcing the fact that relatively few stroke patients are helped by thrombolytics compared to good clinical care. Calixto Machado presented a lecture on the persistent vegetative state (PVS). His research had confirmed that coma, minimally aware states, and PVS were part of a spectrum rather than discrete entities. He provided evidence using quantitative EEG and fMRI that several patients apparently in PVS were in fact "aware" of their environment, at least at a neurophysiological level. Each day was concluded by a teaching session given in Spanish with slides and translation into English. Chris Butler, Ursula Schulz, and Roberto Guiloff gave lectures on epileptic amnesia, posterior circulation ischaemia and chronic inflammatory polyneuropathies.

The highlight was the CPC. Graham Venables bravely took on the challenge of discussing the case of a young Cuban who died after a two week history of headache, confusion and seizures. His review included piracy and the fact that walking the plank never actually happened. He successfully identified the clue that refusal for organ donation in Cuba is very rare unless there is a medical contraindication, but was distracted by the CT scan which was reviewed by neuroradiological colleagues in Sheffield as being consistent with an aneurysmal bleed. The answer was provided by Israel Borrajo the senior neuropathologist at Hermanos Ameijeiras Hospital, as fulminant haemorrhagic

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herpes simplex encephalitis. Graham Venables concluded the CPC by suggesting that he would ask several of his neuroradiological colleagues to reconsider their futures.

Events enjoyed by delegates outside the conference included several concerts of Cuban and other South American music, lunch with Mojitos, and a visit to the Cuban Neurosciences Centre. Individual research units are organised so that basic research, development, production and marketing are all done under one roof. Several of the UK delegates took the opportunity of touring the island, which for Ursula involved a 1000km ride on her bicycle.

During the week, some of the British delegation visited the neurology wards, neurophysiology department and intensive care facilities of the Hospital Hermanos Ameijeiras. Professor Rossor was in his element in examining a man with frontotemporal dementia. We all agreed that neurologists share a common bond of communication transcending language barriers.

This conference brought the largest foreign delegation ever to a Cuban neurological meeting. It was a wonderful opportunity for Cuban and British neurologists to meet and share ideas, and a promising start to future interchanges. ♦



UK delegates outside the Hotel Nacional de Cuba.

2010 Lectures in Neurosurgical Anatomy

Details: 11th and 12th of December, 2010 at Magdalene College. **Report by:** Fardad Afshari and Tom Santarius, 'Department of Neurosurgery, Addenbrooke's Hospital, Cambridge, UK.

Cambridge Lectures in Neurosurgical Anatomy (CLNA) are one of the unique events that take place annually over a weekend in one of the many historic colleges in Cambridge University. This two-day weekend course is open to neurosurgeons and trainees within the UK and outside. Its affordable price (£190 in 2010) and world-class neurosurgical masters and speakers make this a great opportunity for learning relevant surgical neuroanatomy.

Knowledge of anatomy is the basis of surgery and a perfect knowledge of surgical anatomy should be a life-long goal of each surgeon. This is especially true for neurosurgery where the surgical access routes are narrow, the brain and surrounding structures cannot be moved, and the consequences of a mistake disastrous.

The Lectures were initiated six years ago by Mr Ramez Kirolos and Mr Thomas Santarius both neurosurgeons in Cambridge University's Addenbrooke's Hospital with the aim to inspire the generation of young neurosurgeons to perfect their understanding of anatomy of neurosurgical lesions and relevant surgical approaches. Use of three dimensional images of anatomical preparations and intra-operative situations in this course offers highly informative, time and cost effective educational experience far surpassing conventional two dimensional images of surgical preparations and in some ways even cadaveric dissections, to which, however, it best serves as a complement.

One of the other salient features of CLNA is the lectures by the invited world-renowned neurosurgical masters who present their experience as well as novel new techniques and approaches. The lecturers discuss advances and perfection of their techniques aimed at increasing the precision and accuracy of

neurosurgery and improving the outcomes and safety for the patients.

Previous international invited speakers have included professors Guilherme Ribas (Sao Paulo), Hughes Duffau (Montpellier), Fred Gentili (Toronto), Robert Reisch (Zurich), Evandro de Oliveira (Sao Paulo), Nicolas de Tribolet (Geneva), Ugur Ture (Istanbul) and Gazi Yasargil (Little Rock).

2010 Lectures in Neurosurgical Anatomy

Last year's event took place on 11th and 12th of December at Magdalene College. Following a welcome by the course organisers, Mr Ramez Kirolos and Mr Thomas Santarius, and a brief history of the college, the two-day course started off by lectures on surface anatomy of the brain followed by analysis of deeper structures including basal ganglia and ventricles. The anatomy lectures were delivered by Professor Guilherme Ribas, a leading neurosurgeon and neuroanatomist from the University of San Paolo School of Medicine in Brazil. Using three dimensional images and projections of some of the world-best dissection and prosections of the brain prepared in the laboratory of Professor Ribas, important topics on neurosurgical anatomy were revisited.

The emphasis was placed on anatomical identification and intraoperative orientation using the nearby structures, i.e. topographical anatomy. The ever increasing use and reliance on image-guidance in neurosurgery is paralleled by decline of the neuroanatomical knowledge. While recognising the enormous advantage of the neuronavigation in neurosurgery, the Lectures aim at reversing this decline of working anatomical knowledge of neurosurgeons.

The first day of the course was ended by the annual Lectures' dinner at Peterhouse, the oldest Cambridge college.

The second day of the course started with a neurosurgical anatomy quiz that served as a good opportunity to revisit and revise the essential neurosurgical anatomy. Each question was then discussed by Mr Kirolos and Mr Santarius using 3D images from the acclaimed Dr Albert Rhoton collection, donated to the Lectures by the author. This was followed by lectures by Professor Hughes Duffau, Chairman and Director of the Institute of Neurosciences of the University of Montpellier in France. In a series of exciting and mind-opening lectures, Professor Duffau delivered a great account of the management of low grade gliomas and the use of functional mapping of cortex and white matter during tumour resection. Using his own cases, he demonstrated the recent advances in intraoperative brain mapping and how they have minimised injury to crucial functional pathways. The excellent outcomes enjoyed by his patients were not only due to the surgery itself, but due to the understanding of functional anatomy emphasising the role of neuroplasticity and rehabilitation in recovery following tumour resection. In addition he highlighted the advantages of a multi-disciplinary team approach in identifying eloquent areas intraoperatively and how to tailor the surgical procedure for the patient's specific needs.

2011 Lectures in Neurosurgical Anatomy

This year's event is taking place on the 18th and 19th of June at Emmanuel College. The guest speakers will include Professor Guilherme Ribas from the University of San Paolo School of Medicine who will be delivering the anatomy lectures and Professor Jacques J. Morcos from the University of Miami, USA who will deliver the second day lectures focusing on the surgical management of skull base pathology, especially tumours and aneurysms. ♦

PREVIEW: Parkinson's 2011, Epilepsy in Children and Stroke 2011

We are delighted to announce three neuroscience conferences taking place in London in June and July 2011: Parkinson's 2011, Epilepsy in Children and Stroke 2011.

Now in its 13th year, **Parkinson's 2011** (21st June 2011), in conjunction with Parkinson's UK, is an integral meeting in the calendar of health and social care professionals involved in the clinical management of people with Parkinson's. It is designed to provide a state-of-the-art update on current clinical developments in the field.

The main conference themes cover pre-symptomatic markers of Parkinson's, current and emerging pharmacotherapies, an update on the Parkinson's audit and clinical management of non-motor symptoms including swallowing dysfunction, speech problems and anxiety and depression.

Key speakers include: Professor Chris Hawkes, Honorary Professor of Neurology, London; Professor David Burn, Professor of Movement Disorder Neurology, Newcastle; Dr Dorothy Robertson, Consultant in Care of the Elderly, Bath.



Epilepsy in Children (23rd June 2011) presents an excellent opportunity for specialists in neurology, neurosurgery and paediatrics, as well as GPs and specialist nurses to extend their knowledge on the current issues and latest developments in the diagnosis and treatment of paediatric epilepsy.

Highlights of the conference will include reviews of the latest genetic research in paediatric epilepsy, opinions on optimal investigations to use in the diagnosis of epilepsy in children, updates on the effects of long-term use of anti-epileptic drugs and the importance of monitoring drug use in children.

Key speakers include: Professor Sanjay Sisodiya, Professor of Neurology, London; Dr Colin Ferrie, Consultant Paediatric Neurologist, Leeds; Dr Mary O'Regan, Consultant in Paediatric Neurology, Glasgow

Stroke 2011 (7th July 2011) is designed to provide research updates into the diagnosis,

treatment and rehabilitation of stroke.

Key topics will include the importance of early diagnosis and treatment of stroke, assessments of medications and interventional therapies for the prevention of stroke after atrial fibrillation, complications of acute stroke including aphasia and visual and cognitive impairments as well examinations of current and novel stroke treatments.

Key speakers include: Dr Joe Harbisen, Joint National Clinical Lead in Stroke Medicine, Dublin; Dr Matthew Fay, General Practitioner, Yorkshire; Dr Irina Savelieva, Lecturer in Cardiology, London. ♦

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Positive Steps in Parkinson's Disease

Conference details: 4-5 March, 2011, Newcastle, UK. Reviewed by: Professor David Burn and Dr Douglas MacMahon.

The fourth Positive Steps in Parkinson's Disease meeting, sponsored by Teva Pharmaceuticals Ltd and Lundbeck Ltd, was held on March 4-5th in Newcastle. The presentations and discussions covered all aspects of Parkinson's disease (PD), from how clinical research can inform daily practice to practical advice for the diagnosis and management of common PD symptoms. In addition, there were interactive workshops looking at how the forthcoming changes in NHS commissioning might affect PD care, as well as insights into the patient experience. The common theme of the meeting was the need to treat the whole patient rather than just focussing on immediate symptom control and the recognition that treatment decisions in early disease can impact later disease management.

Dr Carl Clarke began the programme by critiquing recent clinical trial data. One hot topic is whether there is a benefit in initiating treatment early in the disease. Dr Clarke reported that a recent meta-analysis of the rasagiline TEMPO and ADAGIO studies and the pramipexole PROUD study found that the evidence supported a statistically significant benefit for rasagiline, but not for pramipexole. He emphasised that it is up to physicians to decide whether the benefits observed are enough to change their clinical practice, and he stressed the need for longer-term studies to evaluate the cumulative benefits of early treatment on long-term disease progression. Dr Clarke then reviewed the data from the STRIDE study. Although the study did not support the early use of Stalevo to prevent dyskinesia, it did highlight how early treatment options can affect later decision-making. For example, patients already receiving a dopamine agonist were at greater risk of developing dyskinesia when Stalevo was initiated compared with those who were not. However, it is important to note that the patients receiving dopamine agonists tended to be younger and therefore already at greater risk of developing dyskinesia, and that the trial design did not permit matching of levodopa dose equivalents (LDE) between the two groups. Indeed, patients receiving Stalevo tended to be on higher LDE than those receiving Sinemet. The importance of dosing levels was again highlighted as Dr Clarke compared the evidence for the prolonged release formulations of pramipexole and ropinirole with their immediate release predecessors. While the data appear to favour the prolonged release formulations, especially for nocturnal problems, patients in the prolonged release studies tended to be titrated to higher doses of agonist than reported in the immediate release studies. Dr Clarke closed his presentation with the news that the large, prag-



Dr Roger Barker discussing the prodromal phase.

matic PD-Med study will start to release details of its first results later this year.

The next presentation moved even earlier in the course of PD where Dr Roger Barker discussed the prodromal phase. The Braak hypothesis of neuronal pathology staging is now widely used as a conceptual framework, and the idea that non-motor symptoms such as hyposmia and sleep dysregulation often develop before motor symptoms is already starting to change clinical practice – many physicians now ask about sleep problems when taking an initial patient history. In contrast, the idea that PD may be a prion disorder is still hotly contested, however, studies now indicate that abnormal pathology in one cell can propagate and affect its neighbouring cells. In addition, Dr Barker stressed that drug treatments are not the only things to consider at diagnosis; increasing evidence supports the benefits of lifestyle changes. For example, it has recently been shown that exercise increases levels of BDNF, which plays an important role in supporting dendritic connections. Similarly, taking omega 3 supplements has been shown to increase levels of GDNF and provide protection against MPTP neurotoxicity in PD animal models.

Dr Paul Worth discussed the needs of patients with advanced PD. He defined this as

when patients have developed troublesome motor complications that affect quality of life. Wearing-off is often the first motor complication to emerge and, in practice, there are three drug classes to consider. The dopamine agonists have been shown to be effective, but their long-term acceptability remains to be evaluated and there is increasing awareness of unwanted effects e.g. impulse control disorders. Dr Worth also discussed the role of MAO and COMT inhibitors: while the evidence for selegiline in treating advanced PD is poor, there is evidence that rasagiline is as effective as entacapone in increasing ON time and reducing OFF time. He reminded the meeting that despite the need for liver monitoring, tolcapone is now worth reconsidering in entacapone-failures before resorting to other advanced options. The presentation concluded with a discussion of the use of Duodopa in patients with refractory motor complications. Although the current trial data is not robust, Dr Worth has found that Duodopa can be very effective. However, physicians considering Duodopa will also need to be aware of the surgical complications, tube complications and replacements associated with this treatment.

Delegates were also invited to interact in parallel sessions where Dr Nin Bajaj and Ms Fiona Lindop discussed the management of

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marketing in patients treated concomitantly with antidepressants/SNRIs and rasagiline. Avoid concomitant use with fluoxetine or fluvoxamine. Leave at least five weeks between discontinuation of fluoxetine and initiation of treatment with rasagiline. Leave at least 14 days between discontinuation of rasagiline and initiation of treatment with fluoxetine or fluvoxamine. Administer potent CYP1A2 inhibitors with caution. Co-administration with dextromethorphan or sympathomimetics not recommended. Avoid use in patients with moderate hepatic impairment. Use caution in patients with mild hepatic impairment. Use with caution in pregnancy or lactation. There is an increased risk of skin cancer in Parkinson's disease, not associated with any particular drug. Suspicious skin lesions require specialist evaluation. Cases of elevated blood pressure have been reported in the post-marketing period, including rare cases of hypertensive crisis associated with the ingestion of unknown amounts of tyramine. **Undesirable effects in clinical trials:** **Monotherapy:** >1%: headache, influenza, skin carcinoma, leucopenia, allergy, depression, hallucinations, conjunctivitis, vertigo, angina pectoris, rhinitis, flatulence, dermatitis, musculoskeletal pain, neck pain, arthritis, urinary urgency, fever, malaise. <1%: decreased appetite, cerebrovascular accident, myocardial infarction, vesiculobullous rash. **Adjunct therapy:** >1%: dyskinesia, decreased appetite, hallucinations, abnormal dreams, dystonia, carpal tunnel syndrome, balance disorder, orthostatic hypotension, abdominal pain, constipation, nausea and vomiting, dry mouth, rash, arthralgia, neck pain, decreased weight, fall. <1%: skin melanoma, confusion, cerebrovascular accident, angina pectoris. **Please refer to the SmPC for the rates of adverse events.** **Basic NHS Price:**

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References:

1. Olanow CW, Rascol O, Hauser R et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *N Engl J Med* 2009; 361: 1268-1278.
2. Stocchi F, Brooks DJ, Melamed E, et al. Effect of rasagiline on severity of OFF in Parkinson's disease. Poster presented at the 58th American Academy of Neurology Annual Meeting, San Diego, California, USA. 2006.
3. Azilect Summary of Product Characteristics. October 2010.



freezing and falls, and Dr Diane Playford discussed neurorehabilitation strategies. Both presentations highlighted the advantages of building a close inter-disciplinary team. For example, whereas freezing is relatively insensitive to current treatments, physiotherapists can help patients to understand how their environment affects their ability to dual task (e.g. walking and talking) and help them find strategies to avoid freezing or use cues to achieve their daily tasks. The audience interaction continued with a discussion of tremor case studies led by Dr Paul Jarman who advised having a 'protocol' in mind when first examining a patient with tremor. A systematic approach that evaluates for rest tremors, posture (looking for dystonia), movements and the ability to complete tasks such as the Archimedes spiral, often helps in the differential diagnosis between essential tremor, dystonic tremor and parkinsonian tremor. Dr Richard Genever also used case studies to promote awareness and planning for PD emergencies. This includes awareness of NMS-like syndromes for which Dr Genever advises having rotigotine patches available in MAU and ITU for acute admissions and/or using a nasogastric tube to administer PD medications and to be aware of other problems such as dopamine dysregulation (DDS) and neuroleptic-malignant syndrome (NMS). When the delegates were asked whether they thought that their substance abuse teams knew about DDS and how to manage it – the answer was mostly 'no'. Continuing with the theme of unusual case studies, Dr Romi Sahar suggested that when faced with complicated cases, physicians need to be able to take a step back and think of possible non-PD diagnoses. In the geriatric population, small vessel disease can often present as primary progressive freezing of gait and the judicious use of scans and continued follow-up can often help in the differential diagnosis.

Sleep disorders are a common problem that can affect patient and carer quality of life, and Dr Paul Reading used his presentation to discuss the need for to be prepared to see the full spectrum of possible sleep disorders within their PD patient population. For example, approximately 20% of PD patients will have RLS, many will have sleep fragmentation and some will have nocturia. REM behavioural disorder (RBD) is also common in PD patients (especially males) and causes recurring, often 'explosive' nightmares and characteristic 'acting out of dreams'. It is now known that dopamine is a key mediator in maintaining sleep-wake cycles and that dopaminergic drugs can induce somnolence. Indeed



excessive daytime sleepiness (EDS) is relatively common in PD, but the patients themselves are poor at recognising it and physicians should try to get information from spouses and carers about patients' sleeping habits. Once a sleep disorder is recognised, Dr Reading advised considering the relationship of the problems to current treatment, RLS and other treatable causes such as sleep apnoea. He cautioned that overnight tests are not always helpful in guiding treatment options and that it is always important to tailor sleep treatments to the patient's individual circumstances.

Continuing the non-motor theme, Dr Clare Fowler discussed the significant impact urogenital symptoms can have on people with PD. Dr Fowler reminded the audience that early bladder or erectile dysfunction should be considered a red flag for MSA and suggested that sphincter EMG can help in the differential diagnosis between the two conditions. Whereas the urinary symptoms of MSA are treatable, they are more difficult to manage in PD and the most troublesome symptom is nocturia. It is important to note that bladder disturbances are highly associated with disease progression and will add to the overall disability of the patient. When considering the patient with urogenital symptoms, Dr Fowler advised first excluding treatable causes, then cautious treatment with antimuscarinics that do not cross the blood-brain barrier and close communication with urologists.

Of all the non-motor problems in PD, one receiving considerable recent attention is impulse control disorders (ICDs) and Dr Iracema Leroi gave an update of work recently conducted in this area. The large observational DOMINION study conducted in over 3000 patients in the United States and Canada has recently been published and has found

that 14% of patients with PD had at least one ICD, and 36% of these had more than one disorder. The study showed that patients with ICDs were generally younger and that ICDs are often associated with depression, anxiety and sleep disturbances. The types of ICD encountered in PD (gambling and hypersexuality are the most common), and patients do not generally show kleptomania or other psychiatric disorders. The DOMINION study showed that both levodopa and dopamine agonists increase the risk of an ICD, but combination therapy with both levodopa and a dopamine agonist increases the risk by 50%. Interestingly, there was little correlation between the dose of dopamine agonists or levodopa and the development of ICDs.

Professor Peter Jenner closed the meeting by bringing together many of the themes that had been discussed over the past two days. He argued that the teaching of PD in medical schools is still based on 'dogma' and needs updating. Young doctors coming through the system need to be aware that PD is a complex illness including motor and non-motor symptoms; that it affects both the central and peripheral nervous systems and that there are a number of clear parkinsonian subtypes which can be defined by symptoms (e.g. tremor predominant versus PIGD) and by the age of onset. The PD armamentarium has never been so full, but physicians need to take the long-term view and think 'strategically' at how to use the available drugs to improve the long-term management. This will mean trying to identify patients as early as possible, as well as treating them for both symptom control and the prevention of further maladaptive changes in the basal ganglia.

Participants left eagerly looking forward to the next meeting planned for 9-10 March, 2012 in London. ♦

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EDITOR'S CHOICE

Silencing genes using exosomes

One of the great challenges in the field of novel therapeutics for genetic disorders affecting the CNS is how you can deliver short interfering RNA (siRNA) to the brain to selectively silence the mutant gene product, and in this new paper this has been done using exosomes. Exosomes are endogenous nanovesicles that transport RNAs and proteins between cells and as such could be useful for the delivery of therapeutic agent, if they can be targeted to the appropriate cell type. In this paper the group of Matthew Wood have shown:

- (a) Exosomes (88nm in diameter) can be harvested with a high degree of efficiency from immature dendritic cells and produce no immune response when injected in vivo or with in vitro T-cell assays;
- (b) The exosomes can be targeted to neuronal and muscle compartments using two different peptides attached to the exosomes – muscle specific peptide (MSP) and

rabies viral glycoprotein (RVG);

- (c) These exosomes can also be loaded efficiently with different siRNAs and seem to work to knock down the appropriate gene product in vitro and in vivo;
- (d) In vivo this silencing occurs in neurons; oligodendrocytes and microglia and their precursors and seems not to involve other non-targeted organs such as the liver, spleen and kidney.

This paper is therefore an exciting new development and could have major implications in the treatment of CNS disorders given that the delivery agent is non-immunogenic and can be isolated easily and engineered with a high degree of target specification. – **Roger Barker.**

Alvarez-Erviti L et al. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. Nature Biotechnol. 2011;29,341-345.

Seizures and the risk of subsequent brain tumour

It has long been known that epilepsy may be the harbinger of CNS tumours. In the era before neuro-imaging was standard, many lesions only manifested with neurological deficits a decade or more after seizure onset. These authors have undertaken an elegant study, quantifying the problem. They looked at two cohorts. The first is an Oxford based cohort, studied from 1963 to 1998, so largely preceding modern neuroimaging and the second a nationwide database, recruited from 1999-2005, when most incident epilepsy cases would have had some form of imaging. In the Oxford Cohort, there were 11,904 patients with a first presentation to hospital with epilepsy and in the national cohort, there were 100637 patients. They excluded patients who already had a tumour when they presented with seizures or were identified to have a tumour in the first year after epilepsy diagnosis, in case subtle lesions were present but missed at first investigation. The rate ratio was calculated as the rate of development of cerebral tumour in patients with epilepsy, compared to control patients with a variety of common non-neurological conditions; ENT, orthopaedic etc. The ratios were remarkably similar in the two cohorts, about 8 times as likely to have any kind of cerebral tumour, and about 25 times as likely to have a malignant tumour. The ratio was highest in the 15-44 year age group, perhaps reflecting that tumour, alcohol and trauma are the three commonest causes of seizure in this age group. The interval from epilepsy to tumour diagnosis was also calculated using the measure of the expected ratio. In the Oxford study, the ratio in the first 4 years was 17.1 (12.2-23.7) and in the national study 8.32 (7.22-9.54). From years 5-14 the ratio was 6.53 in the Oxford Study and beyond year 15 the ratio was 3.29. In studies such as this, the difficulty is often that the individual case data are very limited but this must, at least in part, be offset by the very large number of cases and the consistency of the two studies.

Neuroimaging emerged as a requirement for the investigation of first seizure, during the observation periods of this study, firstly

CT and then MRI. This may mean that these broad cohorts hide some heterogeneity with earlier diagnosis toward the end of the period. However, even in the national group, when most patients would have had some sort of imaging at presentation, there is a large number who had a diagnosis of tumour at some time later. So what is happening here? Are there microtumours, not initially visible? We should be used to this from the tiny cortical dysplasias, which can cause epilepsy, and are invisible, even on standard MRI. Or are there other factors which predispose to both epilepsy and tumours? Some studies have also shown an increased risk of non-cerebral malignancy in patients with epilepsy, but not with these high ratios. Does epilepsy cause tumours? I suspect that if this were the case, then the risk of tumour would increase with the duration of epilepsy, whereas the ratios fall with time in this study. The authors recommend maintained vigilance for the possibility of developing a tumour – sound counsel. But before we get too alarmed, it is worthwhile remembering that in two cohorts amounting to something approaching a million patient years (my estimate), there was an excess of about 300 tumours (roughly one in 3,000 patient years). How many have you seen?

– **Mark Manford.**

Khan T, et al. Epilepsy and the subsequent risk of cerebral tumour: record linkage retrospective cohort study. (2011) JNNP epub ahead of print Mar 28.

The epilepsy history in subjects with intellectual disability

The misdiagnosis of epilepsy is a key problem. Good history taking can help to reduce the frequency of mistakes. In a learning disability population one key element of the history may be missing; the story from the patient themselves. In addition, some patients with learning disability may exhibit behaviours which resemble seizures but are not. This study reviewed the literature and reminded us of the difficulties. Each symptom has to be

analysed in its own right and what the carer calls a seizure may not be a seizure, for example in up to 82% of those caring for patients with Rett syndrome. But equally 30% of patients with Rett syndrome had epileptic events which were not identified. In one study, 94% of new events reported as seizures by carers, turned out not to be seizures. Among the things to watch out for: stereotypies (especially with swallowing, mimicking partial seizures) and self-stimulatory tics; ataxia or dystonia with falls and periods of inattention. Wake up, what did I say? Yes – inattention.

– **Mark Manford.**

The misdiagnosis of epilepsy in people with intellectual disabilities: A systematic review. Chapman M, Iddon P, Atkinson K, Brodie C, Mitchell D, Parvin G, Willis S. *Seizure* 2011;20:101-106.

Clues from B cell depletion in Devic's disease

A study from the Institute of Clinical Neuroimmunology at Munich gives much needed prospective data on the use of rituximab in Devic's neuromyelitis optica. A study of 10 patients, it provides useful safety data and suggestive biomarker data, though as expected, is biased towards severe refractory disease with high disability. The patients were young (range 16-45), had clinically definite disease (as defined by Wingerchuk et al. *Neurology* 2006) and had a baseline Kurtzke Expanded Disability Status Scale (EDSS) score range of 1.5 to 8.5/9, with 6 at or above EDSS 6, 2 at EDSS 8 or above). The patients had disease refractory to at least one immunosuppressant or immunomodulatory agent (4 azathioprine, 1 cyclophosphamide, 2 IVlg, and interestingly 4 beta-interferon, 1 mitoxantrone, 2 copaxone, and 1 natalizumab, indicating that diagnostic confusion with multiple sclerosis was initially apparent in many cases). Most patients received 4 or 5 repeated courses of rituximab. The annualised relapse rate (with follow up range of 0-45 months) was reduced in 8 of the 10 patients. 1 patient didn't respond to the drug and another with Sjögren's syndrome and baseline EDSS of 8.5/9 died shortly after the 1st course. The other 3 patients who relapsed did so after reappearance of B cells, but there was no clear relationship to AQP4 antibody titres or B-cell-fostering cytokines (BAFF and APRIL). Six developed severe infections. Putting aside the problems with historical control data in a prospective study, randomised controlled trials of this drug in a broad range of central and peripheral neuroimmunological diseases are warranted. The question remains whether to focus such trials on homogeneous refractory groups, or bite the bullet and go for large heterogeneous studies in subjects with early disease and limited disability.

– **Mike Zandi.**

Pellkofer HL, et al. Long-term follow-up of patients with neuromyelitis optica after repeated therapy with rituximab. *NEUROLOGY* 2011 Apr 12; 76:1310-5.

Just my imagination

The concept (if not the practice) of motor imagery is fairly well embedded in the current thinking around neurological rehabilitation, especially within the context of stroke. The idea of neural circuits involved in the imagining of a particular task influencing or interlinking with those circuits actually involved in the execution of the task is established in the field of sports training and becoming more so in the design of new treatment paradigms for brain injury

and cerebrovascular disease. Of course, the ability to imagine an abstract movement, even at a very functional level is dependant upon a number of other processes being intact. The ability to understand instructions pertaining to a particular task may be significantly impaired by a language deficit. Even at a non-verbal level the restrictions imposed upon communication by, for example, visual field or working memory problems will limit the usefulness of mental imagery in a clinical context.

Non-dominant hemisphere strokes with consequent sensory neglect and attentional deficits can be particularly challenging. Professionals treating patients with non-dominant hemisphere lesions need to be aware of the particular problems faced by this patient group. One, especially in the early stages of rehabilitation within this patient group, is the lack of spatial awareness. Trying to improve the function of a hemiparetic limb is hard if the owner of said limb has difficulty in realising its existence. Is there a place for motor mental imagery in this patient group? The question is addressed in this study by focusing on a relatively small group of patients with non-dominant hemisphere lesions who have left hemispatial visual neglect. The control group have right hemispheric lesions without neglect. Both groups were subject to a test of mental imagery in a visual context (pictures of left or right hands presented at different angles with the patient being asked to rapidly assess which hand is being shown) and a verbal context (a questionnaire asking the subject to generate a mental image of a hand and then correctly identify where the thumb and little finger are).

The group with hemisensory neglect performed significantly less well than those without neglect on a motor imagery task based on visual input. Interestingly both groups perform poorly when the task is based on verbal instructions. This is a somewhat unexpected finding, but needs validation in comparison with a patient group with dominant hemisphere strokes. While there are opportunities and further areas of development within the field of motor imagery, the potential pitfalls of using a visual or verbal approach for specific patient groups needs to be considered. Unfortunately the small size of this study and the lack of information on handedness (there is an assumption that the right hemisphere is non-dominant for all patients) does limit the wider conclusions that can be drawn. Nevertheless, the importance of tailoring rehabilitation strategies to the needs of an individual rather than diagnostic group is a point that bears repeating.

– **Lloyd Bradley, Western Sussex Hospitals.**

Vromen A, et al. Motor Imagery in Patients with a Right Hemisphere. Stroke and Evidence of Neglect. *BRAIN INJURY* April 2011;25(4):387-393.

Driving with non-epileptic attacks

The DVLA says for patients with psychogenic non-epileptic seizures: "licence will be issued after medical reports confirm that behavioural disturbances have been satisfactorily controlled". Personally, I appreciate the suitable vagueness of the guideline which allows me to use driving as a carrot to try and engage with the patient and help them towards a recovery. But how many UK neurologists know about this? Of 54 responding to an email, 43 did. When asked what neurologists thought the regulations should be, there was a resoundingly random response, ranging from the same as epilepsy to no restriction at all. So, when is it better? Given the high frequency of attacks in most patients with PNES, one can usually say quickly if it has gone into remission and if it is not 100% remission, does it matter? Does it really cause accidents in the same way as epilepsy? Well two respondents said they had patients where it did.

– **Mark Manford.**

Driving regulations and psychogenic non-epileptic seizures: perspectives from the United Kingdom. Morrison and Razvi. *SEIZURE* 2011;20:117-80.

First oral treatment for highly active relapsing remitting MS for UK patients

The first oral treatment for multiple sclerosis (MS) is now available in the UK. Fingolimod 0.5mg (Gilenya™) has been authorised for people with highly active relapsing remitting multiple sclerosis (RRMS) who have failed to respond to an interferon (injection), or for those with rapidly evolving severe disease.

Fingolimod provides a treatment option for patients failing on injections but whose disease is not severe enough for infusion therapy. Patients on an interferon need to have had one or more relapses within the last year to be eligible for treatment with fingolimod.

Fingolimod is a new class of drug called a sphingosine 1-phosphate (S1P) receptor modulator

that works in a completely different way to any other MS treatment. As fingolimod is an immunomodulator, it does not kill lymphocytes but retains them in the lymph nodes thereby preserving key immune functions.

Fingolimod is available to appropriate patients in the UK and neurologists can apply for treatment reimbursement via individual funding requests. NICE is currently reviewing fingolimod and will issue draft guidance in July 2011.

For more information contact Novartis on Tel. +44 (0)1276 698 691.

Innovations for imaging and diagnostics

Siemens Healthcare presented innovations for imaging and diagnostics at the European Congress of Radiology 2011. Highlights included the Biograph™ mMR, the world's first integrated whole-body molecular MR with simultaneous data acquisition technology, and two new radiography systems: the MULTIX Select DR and the Mobilett Mira. Siemens also showcased its image management and diagnostic software syngo[®]via.

The Biograph mMR has the potential to provide new diagnostic opportunities in neurology, as well as opening up new opportunities for research. It comprises a 3-Tesla magnetic resonance (MR) scanner and an integrated positron emission tomography (PET) detection system, making it possible to simultaneously capture MR and PET data with a whole-body system for the first time. While MR provides intricate morphological and functional details in human tissue, PET goes further to investigate the human body at the level of cellular activity and metabolism.



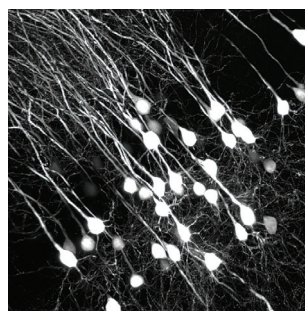
The MULTIX Select DR is an entry-level X-ray system that facilitates cost-effective access to Digital Radiography. The Mobilett Mira is Siemens' first mobile digital X-ray system with a wireless detector. syngo.via, Siemens' imaging software for multimodality reading of clinical cases, has advanced visualisation tools and automated processes helps increase reading efficiency across multiple specialities.

For more information contact Siemens Healthcare on Tel. +44 (0)1276 696374

Nikon introduces streamlined A1 MP imaging system

Nikon has developed a streamlined version of its AIR MP multiphoton confocal imaging system. The new A1 MP scanner has been developed for simplified, cost-effective multiphoton imaging, whilst maintaining the sensitivity and quality of the highly respected AIR MP system. Multiphoton imaging is becoming increasingly popular for cell-friendly, dynamic live cell and deep tissue imaging but budgetary constraints have, historically, prevented some laboratories from realising the full potential of this technique.

Fluorescence detection is undertaken by Nikon's highly sensitive NDD detectors (Non Descan Detectors). The scanner is capable of



frame rates up to 10 fps, depending on image size and can easily be upgraded to true spectral imaging using Nikon's spectral detector.

The A1 MP imaging system can be used in conjunction with Nikon's upright FNI microscope and inverted Nikon Ti-E microscope, where it can also be combined with a TIRF system and

incorporated with the Perfect Focus System for long term, deep tissue imaging.

For more marketing information on Nikon microscopes please contact Nikon Instruments Europe: Tel. +44 (0)208 2471718 E. info@nikoninstruments.eu, www.nikoninstruments.eu/

Alzheimer's drugs to be made available to all

The National Institute for Health and Clinical Excellence (NICE) recently released its final guidance on four Alzheimer's drugs. The guidance means the drugs Aricept, Exelon and Reminyl will be available on prescription to people in the early and moderate stages of Alzheimer's and Ebixa will be available to people in the late stages. PCTs must now ensure they are providing funding for the drugs by June 2011. This final decision represents a reversal of the position which was in place since 2007 which limited access to drugs to only people in moderate stages.

Sativex[®] improves symptoms of spasticity due to MS



Results from a phase III clinical study published online in the European Journal of Neurology Early View showed that about half of all people with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to standard anti-spasticity therapy, find that adding Sativex[®] Oromucosal Spray (delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)), to their existing medication can improve the debilitating symptoms of spasticity associated with MS.

The primary efficacy endpoint was the change in a validated, 10 point (0-10) self-reported spasticity numerical rating scale (NRS) from the point of randomisation to the end of the treatment. Sativex[®] was shown to provide significant improvement, compared to placebo, in the NRS spasticity score, spasm frequency and sleep disturbance related to spasticity.

See <http://onlinelibrary.wiley.com/doi/10.1111/j.1468-1331.2010.03328.x/abstract> or www.sativex.co.uk

Epilepsy Society goes purple

Epilepsy Society, formerly the National Society for Epilepsy (NSE), has rebranded and gone purple – the internationally recognised colour for epilepsy. As well as changing its name and colour to purple the charity has also redesigned and updated its website. Bridget Gardiner, Epilepsy Society's Director of Fundraising and Marketing, said, "By simplifying our name and updating our look, we hope to reach out to more people. Our vision is for a full life for everyone affected by epilepsy. In addition, we'll be focusing on some new areas identified during the review of the charity's brand and strategic direction – campaigning in particular. We want to work more closely with people affected by epilepsy to make a real difference."

For more information see www.epilepsysociety.org.uk



Confidence to take action everyday

COPAXONE® (glatiramer acetate)

PRE-FILLED SYRINGE PRESCRIBING INFORMATION

Presentation – Glatiramer acetate 20mg solution for injection in 1ml Pre-filled Syringe. **Indication** – Treatment of patients who have experienced a well-defined first clinical episode and are determined to be at high risk of developing clinically definite multiple sclerosis (MS). Reduction of frequency of relapses in relapsing-remitting MS in ambulatory patients. In clinical trials this was characterised by at least two attacks of neurological dysfunction over the preceding two-year period. **Dosage and administration** – 20mg of glatiramer acetate (one pre-filled syringe) administered sub-cutaneously once daily. **Children (12 – 18 years)** No specific studies. Limited published data suggest the safety profile of 20mg administered sub-cutaneously once daily is similar to that seen in adults. **Children (<12 years)** Not recommended. **Elderly** No specific data. **Impaired renal function** No specific studies. Monitor renal function during treatment and consider possibility of deposition of immune complexes. **Contra-indications** – Known allergy to glatiramer acetate or mannitol (excipient). **Pregnancy. Special warnings and precautions** – Sub-cutaneous use only. Initiation to be supervised by neurologist or experienced physician. Supervise first self-injection and for 30 minutes after. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders and review such patients regularly. Rarely convulsions and/or anaphylactic or

allergic reactions. Rarely, hypersensitivity (bronchospasm, anaphylaxis or urticaria). If severe, treat appropriately and discontinue Copaxone. **Interactions** – No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored. **Pregnancy and lactation** – Not to be used in pregnancy. Consider contraceptive cover. No data on excretion in human milk. **Undesirable effects** – Local injection site reactions (erythema, pain, mass, pruritus, oedema, inflammation, hypersensitivity, injection site atrophy). An immediate post-injection reaction (one or more of vasodilation, chest pain, dyspnoea, palpitation, tachycardia) may occur within minutes, reported at least once by 31% of patients receiving Copaxone compared to 13% of patients receiving placebo. Other undesirable effects more than 2% (>2/100) higher incidence in the Copaxone treatment group than in the placebo group: Nausea, anxiety, rash, back pain, chills, face oedema, vomiting, skin disorder, lymphadenopathy, tremor, eye disorder, vaginal candidiasis, weight increased. Rarely: Anaphylactoid reactions. Please refer to the SPC for a full list of adverse effects. **Overdose** – Monitor, treat symptomatically. **Pharmaceutical Precautions** – Store Copaxone in refrigerator (2°C to 8°C). If the pre-filled syringes cannot be stored in a refrigerator, they can be stored at room temperature (15°C to 25°C) once for up to one month. Do not freeze. **Legal Category** – POM. **Package Quantity and Basic NHS Cost** – 28 pre-filled syringes of Copaxone: £513.95. **Product Licence Number** – 10921/0023.

Further Information – Further medical information available on request from Teva Pharmaceuticals Limited, The Gate House, Gatehouse Way, Aylesbury, Bucks, HP19 8DB. Date of Preparation – December 2009.

Adverse events should be reported.
Reporting forms and information can be found at www.yellowcard.gov.uk.
Adverse events should also be reported to Teva Pharmaceuticals Ltd on telephone number: 01296 719768.

Date of Preparation: February 2011

C0111/673a



COPAXONE®
(glatiramer acetate)

Standing up to RRMS everyday

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